ARCHIVES OF PATHOLOGY

VOLUME 24 DECEMBER 1937 NUMBER 6

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COMPARATIVE HISTOLOGY OF YAWS AND SYPHILIS IN JAMAICA

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It is generally agreed that yaws and syphilis are closely related diseases. There are, however, well recognized clinical and epidemiological features which serve to distinguish one disease from the other. Study of the two diseases among human beings living in the same country and among animals maintained under identical environmental conditions indicates that variations of environment, such as exist between the tropics and the temperate zone, do not determine the essential differences between yaws and syphilis but that these differences are due to inherent biologic differences between the causative agents of the two diseases.[1] As a part of the general problem of the relationship between yaws and syphilis, a study of the histologic features of certain of the cutaneous lesions of each disease has been made. In this paper will be described the histologic features of the common cutaneous lesions of yaws, and a comparison will be made with lesions of similar types obtained from patients with syphilis.

MATERIAL AND METHODS

This study was made on material collected during the course of other studies on yaws in Jamaica, British West Indies. All patients from whom specimens were obtained resided in the rural communities of either Bath or Seaforth or in Kingston, the principal city of Jamaica, and attended the clinic established in their respective community. As patients in the clinic, they were submitted to medical examination as described in a previous paper.[2] Histologic material was collected

Read before the American Society of Tropical Medicine, Nov. 20, 1936.

From the Department of Pathology of Cornell University Medical College and the Jamaica Yaws Commission, the latter operating with the support and under the auspices of the International Health Division of the Rockefeller Foundation and the Government of Jamaica.

1. Turner, T. B., and Chesney, A. M.: Bull. Johns Hopkins Hosp. **54**:174, 1934. Turner, T. B.: Am. J. Hyg. **25**:477, 1937.

2. Turner, T. B., and Saunders, G. M.: Am. J. Hyg. **21**:483, 1935.

TABLE 1.—*Data on Histologic Specimens from Patients with Yaws*

Type of Lesion Studied and Case Number	Race of Patient	Age, Yrs.	Sex	Associated Cutaneous Lesion of Different Type	Estimated Duration of Infection	Previous Antiyaws Treatment	Estimated Duration of Lesion Studied	Result of Dark Field Examination	Titer of Wassermann Reaction*	Treponemes (T. Pertenue) Found in Section
Initial lesion										
1.....	Black	9	M	Frambesiform lesion	4 wks.	No	4 wks.	Positive	3	Many
2.....	Black	13	F	Scaly macules	2 mos.	No	2 mos.	Positive	6	None
Scaly macules										
3.....	Black	8	F	Initial lesion, plantar hyperkeratosis	2 mos.	No	3 wks.		4	Few
4.....	Black	9	F	Initial lesion, plantar papule	2 mos.	No	3 wks.		Positive	Moderate number
5.....	Brown	5	F	Plantar hyperkeratosis	2 yrs.	Yes	4 mos.		Positive	None
Folliculopapules										
6.....	Black	11	M	Initial lesion	2 mos.	No	2 wks.		5	Moderate number
7.....	Black	8	F	Initial lesion, frambesiform lesion	2 mos.	No	1 wk.	Positive	5	None
8.....	Black	12	M	Initial lesion, frambesiform lesion	3 mos.	No	2 mos.		6	
9.....	Black	8	M	Initial lesion	3 mos.	No	2 mos.		3	None
10.....	Black	11	M	Initial lesion	4 mos.	No	2 wks.		Positive	Few
11.....	Black	12	M	None	2 yrs.	Yes	6 mos.		4	None
12.....	Black	7	F	Plantar papule	2 yrs.	Yes	1 mo.		Positive	None
13.....	Black	24	F	Frambesiform lesion, plantar hyperkeratosis	6 yrs.	Yes	3 wks.		2	None
14.....	Black	14	M	None	9 yrs.	Yes	6 mos.		Positive	Few
Frambesiform lesion										
15.....	Black	16	F	Initial lesion, scaly macules	1 mo.	No	1 wk.	Positive	5	Many
16.....	Black	8	F	None	3 mos.	No	2 mos.	Positive	5	Many
17.....	Black	8	M	Initial lesion, plantar papule	3 mos.	No	1 mo.	Positive	7	Many
18.....	Black	25	M	Initial lesion	3 mos.	No	1 mo.	Positive	5	Many
19.....	Black	16	M	Initial lesion, folliculopapules	3 mos.	No	1 mo.	Positive	Positive	Many
20.....	Black	12	M	Initial lesion, folliculopapules	3 mos.	No	2 mos.	Positive	6	
21†.....	Yellow	7	M	Scaly macules, folliculopapules	3 mos.	No	2 mos.	Positive	Positive	Many
22.....	Black	11	M	None	6 mos.	No	2 mos.	Positive	Positive	Many
23†.....	Black	11	F	Scaly macules, folliculopapules	1½ yrs.	Yes	3 mos.	Positive	Positive	Many
24.....	East Indian	16	M	Plantar hyperkeratosis, folliculopapules	4 yrs.	Yes	1 mo.	Positive	Positive	Many
Plantar papule										
25.....	Black	13	M	Folliculopapules	5 yrs.	Yes	3 mos.	Positive	5	Many
Late hyertrophic lesion										
26.....	Brown	13	F	None	1 yr.	Yes	5 mos.	Negative	Positive	None
27.....	Black	15	M	Lesion of bone	4 yrs.	Yes	1½ yrs.		Positive	None
Late destructive lesion										
28.....	Brown	5	F	Multiple lesions of bone	2 yrs.	Yes	3 mos.	Negative	Positive	None
29.....	Black	11	F	Lesions of bone	3 yrs.	Yes	1 yr.	Negative	Positive	None
30.....	Black	11	M	None	3 yrs.	Yes	1 yr.		5	None
31.....	Black	12	M	Plantar hyperkeratosis	9 yrs.	Yes	4 mos.	Negative	Positive	Few
32.....	Black	20	F	Late hypertrophic lesion	16 yrs.	Yes	3 mos.	Negative	4	Moderate number
33.....	Black	29	F	Subcutaneous gumma, lesion of bone	18 yrs.	Yes	1 yr.	Negative	7	None
34.....	Black	25	F	None	24 yrs.	Yes	5 yrs.	Negative	Negative	None
35.....	Black	38	F	None	28 yrs.	No	3 yrs.	Negative	Positive	None
36.....	Black	58	F	Gangosa	55 yrs.	No	4 yrs.	Negative	Positive	None
Subcutaneous gumma										
37.....	Black	11	F	Late lesion of skin, lesion of bone	2 yrs.	Yes	3 mos.	Negative	6	None
38.....	Black	29	F	Late lesion of skin, lesion of bone	18 yrs.	Yes	1 yr.	Negative	7	None

* The titer of the reaction is designated by the number of the last tube which showed complete fixation of complement.
† Dr. G. M. Saunders secured the specimen for us in this case.

only from patients in whose cases the diagnosis of yaws or syphilis seemed reasonably definite. Specimens were removed under local anesthesia, and an effort was made to secure a representative section of a lesion of the predominant type when more than one type was present. Tissue specimens were fixed in a solution of formaldehyde U. S. P. diluted 1:10, embedded in paraffin and cut in the usual manner. Sections were stained with hematoxylin and eosin, Mallory's aniline blue, and Verhoeff's stain for elastic tissue and by the Warthin-Starry [3] method of single section silver impregnation for spirochetes.[4]

Specimens of yaws lesions were obtained from patients living in one or the other of the rural communities or in Kingston.[5] Of the latter, all had acquired yaws in some rural district where the disease was endemic but at the time of biopsy were residing in Kingston. With two exceptions, all of the patients with syphilis were residents of Kingston and presumably had acquired the disease in

TABLE 2.—*Data on Histologic Specimens from Patients with Secondary and Tertiary Syphilis*

Type of Lesion and Case Number	Race of Patient	Age, Yrs.	Sex	History or Evidence of Primary Lesion	Estimated Duration of Secondary Lesion	Result of Dark-Field Examination	Titer of Wassermann Reaction*	Spirochetes (S. Pallida) Found in Section
Maculopapular lesion								
1.....	Black	17	M	No	3 mos.	Negative	6	None
2.....	Black	24	M	Yes	4 wks.		6	None
3.....	Black	22	M	Yes	1 wk.	Negative	6	Few
4.....	Brown	13	F	No	2 wks.	Negative	6	None
Papular lesion								
5.....	Black	19	M	Yes	1 wk.	Negative	6	Moderate number
6.....	Black	28	M	Yes	4 wks.	Negative	5	Few
7.....	Black	22	M	No	3 wks.		6	Few
8.....	Black	24	M	Yes	3 wks.	Negative	5	Few
9.....	Brown	27	F	No	3 mos.	Negative	5	Moderate number
10.....	Black	24	M	Yes	3 wks.		5	Few
11.....	Black	19	M	Yes	3 wks.	Negative	4	None
12.....	Brown	44	F	No	2 wks.	Positive	4	Few
13.....	Black	22	F	No	3 wks.	Negative	5	Many
Tertiary lesion								
14.....	Brown	33	M	Yes	1 mo.	Negative	Positive	None

* The titer of the reaction is designated by the number of the last tube which showed complete fixation of complement.

that city. These patients not only presented the classic clinical features of syphilis but gave no history of yaws and probably had not been exposed to infection with yaws, since this disease is acquired rarely if ever in Kingston.

In tables 1 and 2 are given certain pertinent data concerning the specimens which are to be described. The majority of the patients were full-blooded Negroes (black), a few were mixed black and white (brown), one was East Indian, and one was Chinese. The estimated duration of infection is calculated from the development of the initial lesion. The titer of the Wassermann reaction of the blood is

3. Farrier, R., and Warthin, A. S.: Am. J. Syph. **14**:394, 1930.

4. The histologic technic, including the Warthin-Starry preparations, was carried out by Miss Frances Fraser.

5. Dr. A. A. Peat, Medical Officer of Health, Jamaica, formerly assigned to the Jamaica Yaws Commission, rendered assistance during a part of this study.

† Dr. G. M. Saunders secured the specimen for us in this case.

EXPLANATION OF FIGURE 1

A (case 1, table 1), initial lesion of yaws on an ankle. See figure 2 *A*.

B (case 11, table 1), folliculopapules of yaws on the calf of a leg.

C (case 21, table 1), frambesiomas of yaws on the right arm, on the face and beneath the chin.

D (case 22, table 1), frambesioma of yaws on a forearm.

E (case 17, table 1), frambesioma of yaws cut in half; × 2. See figure 5 *C*.

F (case 27, table 1), late hypertrophic lesion of yaws.

G (case 31, table 1), late destructive lesion of yaws.

H (case 33, table 1), late destructive lesions and subcutaneous gumma of yaws.

FIGURE 1

designated by the number of the last tube which shows complete fixation of complement, according to the following tabulation:

Tube	Approximate Amount of Whole Serum in Tube, Cc.
1	0.1
2	0.05
3	0.025
4	0.0125
5	0.00625
6	0.00312
7	0.00156
8	0.00078

CLINICAL COURSE OF YAWS

On infection with Treponema pertenue the human host responds at first in a fairly well defined manner, so that in its early stages yaws follows a somewhat similar course in nearly all infected persons. But after the first few months of the disease, marked variation in the response of patients is noted, and during the succeeding years the clinical course of the disease follows no orderly pattern. The initial, or primary, lesion, which develops at the site of implantation of yaws spirochetes, is characteristically a granuloma, which may heal before generalized lesions appear but usually persists for several months, and eventually the hypertrophic features of the lesion may be replaced by destructive changes not unlike those encountered in later stages of the disease.

Before or soon after the appearance of the initial lesion, treponemes migrate to the regional lymph nodes, and shortly thereafter widespread dissemination by way of the blood stream occurs, initiating the generalized phase of the disease. While treponemes are doubtless carried to virtually all structures of the body, pathologic changes sufficient to produce clinically recognizable lesions usually occur only in the skin and bones. The evolution of the lesions of the skin varies considerably among different persons, but in general the succession of events is somewhat as follows: The first generalized lesions to appear are frequently scattered scaly macules. Within a few days or weeks these are followed by groups of folliculopapules, small isolated papules or typical frambesiform lesions. An extensive rash may develop within two or three weeks and begin to subside within another month, but ordinarily multiple frambesiform lesions persist for several months and may remain without much change for as long as a year. A period characterized by retrogression of lesions then follows. During this period a majority of the lesions heal, but commonly a few frambesiform lesions remain, or recurring crops of small papules are noted. During this period, also, destructive lesions, usually few, may occur. Eventually a stage is reached when the patient is without lesions most of the time. This period, of latency, however, is often punctuated by the occurrence of lesions similar to those observed during the phase of retrogression.

CLINICAL COURSE OF SYPHILIS

In contrast to the rather slow evolution of yaws in the typical case, infection with Spirochaeta pallida Treponema pallidum) commonly gives rise to a disease in which the succession of events occurs much more regularly and with fairly definite relations of time between the various phases. The clinical course of syphilis in the usual case is too well known to need description here. Perhaps the most outstanding difference between yaws and syphilis is the more protracted generalized phase of the former as compared with the latter—probably an expression of the immunologic response of the human organism to the two causative agents. Unfortunately, no practical method is available for measuring the immunity developed during the course of either disease, but it appears from observations on man [6] and animals [7] that resistance to reinfection develops much more promptly in the presence of syphilis than in that of yaws. Perhaps the spirochete of syphilis is a more potent antigen than is that of yaws.

HISTOLOGIC OBSERVATIONS ON CUTANEOUS AND SUBCUTANEOUS LESIONS OF YAWS

1. *Initial, or Primary Lesion.*

The initial lesion of yaws is essentially a granuloma characterized by tissue proliferation. Since, however, the lesion often arises at the site of a preexisting ulcer, both proliferative and destructive changes may be noted. The surface usually presents the corrugations or morulations so characteristic of frambesiform lesions, and indeed the initial lesion at times can scarcely be differentiated from the typical frambesioma which occurs during the generalized phase. Usually, however, it is larger and more irregular. In the absence of treatment, the initial lesion tends to persist for many months, and frequently the hypertrophic lesion is gradually superseded by an ulcer, which in appearance is not unlike the late type of lesion. Until this phase supervenes, the treponemes of yaws can usually be recovered from the lesion without difficulty.

Two specimens are available for microscopic study. Their structure is somewhat different, and they will therefore be described separately.

Epidermis: In the first specimen (table 1, case 1) there is some thickening of the superficial parts of the epidermis, with a moderate amount of keratinization. The rete pegs are hypertrophied and elongated, with irregular branching, especially at or near their deeper extremities (fig. 2 *A*). This hyperplasia produces an elevated papillary lesion. Melanin pigment is much reduced in amount. Small foci of edema are present, the earliest phase being hydropic degeneration of the cells, with separation of the nuclei from the surrounding cytoplasm; where the edematous condition is more advanced, the cells are spread apart and a homogeneous pink-staining material is seen in some areas. In places there is considerable necrosis of the epithelium. Polymorphonuclear neutrophilic leukocytes are seen, particularly in the areas of edema and necrosis of the more superficial epidermis and in rete pegs.

6. Turner, T. B.: Am. J. Hyg. **23**:431, 1936.
7. Schobl, O.: Philippine J. Sc. **43**:583, 1930.

EXPLANATION OF FIGURE 2

A (case 1, table 1), initial lesion of yaws (× 54), showing downgrowth of epithelium with elongation of papillae of dermis. There are areas of edema in the epidermis in the right upper corner of the illustration, with exudation of leukocytes. An infiltration of lymphocytes and plasma cells is seen in the dermis.

B (case 15, table 1), frambesiform papule of yaws (× 54), showing edge of the lesion, with gradually increasing length of epithelial downgrowths. There are leukocytes in the epidermis and dermal papillae, with infiltration of lymphocytes and plasma cells deep in the subpapillary dermis. There is extensive necrosis of the superficial epithelium.

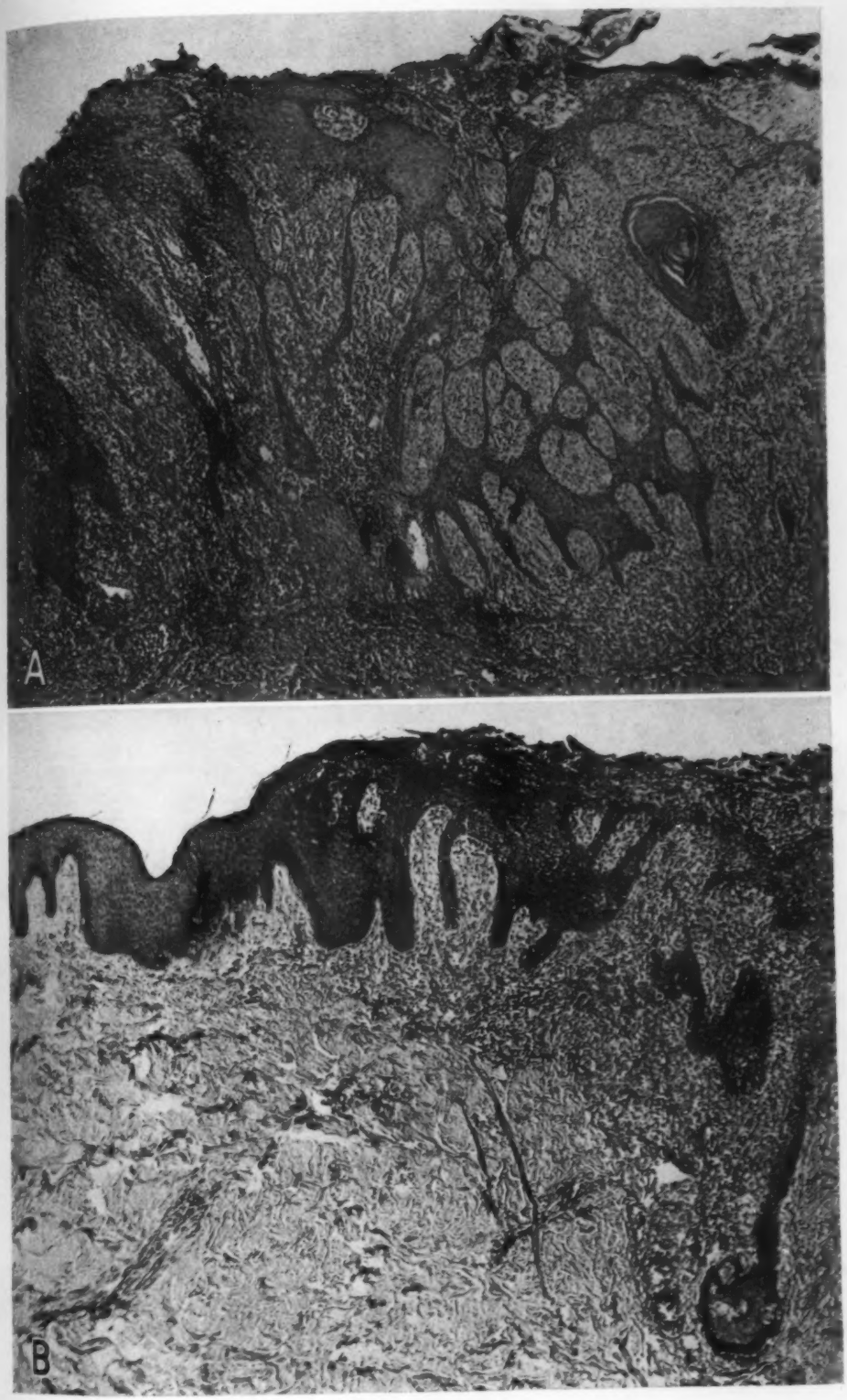


FIGURE 2

Dermis: Edema of the dermal papillae, with dilatation of lymphatic vessels, is present. Capillaries are slightly dilated, and their endothelial cells are somewhat swollen. There is scant proliferation of fibroblasts. In the papillae are a few polymorphonuclear leukocytes, which are more numerous adjacent to the areas of leukocytic infiltration in the epidermis. Occasional eosinophils and a few lymphocytes are seen. Plasma cells are present in larger numbers than cells of other types.

In the subpapillary part of the dermis there is a fairly distinct zone of lymphocytes and plasma cells, which are often abundant about small blood vessels and sweat glands, where there is some associated edema. There are no significant changes in the smaller arteries, though capillaries are numerous.

Spirochetes: Organisms are seen in considerable numbers in the epidermis, especially above the tips of dermal papillae, and in some of the rete pegs. There are also spirochetes in a few areas of necrosis of the more superficial layers of epithelium. They are especially abundant where polymorphonuclear leukocytes are most numerous. The spirochetes appear, in places to lie between the epithelial cells, but there is no evidence that they are present within the substance of any cell. In the papillae of the dermis (fig. 7 *A*) spirochetes are seen in considerable numbers adjacent to foci of conspicuous change in the epidermis; they rapidly diminish in number deeper in the papillae, being rarely found in the lower part and in the subpapillary dermis. While the organisms may lie across fibroblasts, plasma cells, lymphocytes or polymorphonuclears they are not recognized within any of these cells. Indeed, they frequently lie entirely free from cells in edematous areas of the stroma.

The second specimen (table 1, case 2) differs from the first in the following respects: There is more keratinization of the epithelium. Edema is less prominent and occurs only as hydropic degeneration of cells. Plasma cells and lymphocytes are in the dermis in equal numbers and are in scattered groups as compared with the relatively dense subpapillary zone of plasma cells seen in the first specimen. The connective tissue is denser, with areas of young granulation tissue. Spirochetes are not demonstrated.

2. *Generalized Lesions.*

(*a*) *Scaly Macules.*—These lesions are usually irregular patches from 3 to 5 mm. in diameter, appearing white against the dark background of the black skin because of a fine branlike scale. When they are viewed through a hand lens, pinpoint-sized papules can often be seen, and indeed all grades of lesions occur, from macules which cannot be felt to groups of distinct papules such as are described in the subsequent section. At times slight hypertrophy of tissue at the edge of a lesion occurs, producing an annular configuration. Treponemes have not been demonstrated in macular lesions by ordinary dark field examination.

Three specimens (table 1, cases 3, 4 and 5) are studied microscopically.

Epidermis: The epidermis is thickened by an increase of outer layers of cells, with keratinization, and slight hypertrophy of the rete pegs (fig. 3 *A*). Melanin is only slightly reduced in amount. Foci of edema and leukocytic infiltration are small and inconspicuous.

Dermis: There are small areas of edema in the dermal papillae, with a few lymphocytes, fewer plasma cells and only occasional polymorphonuclear leukocytes. In the subpapillary dermis edema is more conspicuous and lymphocytes and plasma cells more numerous. In two specimens are seen several groups of large cells suggesting epithelioid monocytes. The inflammatory reaction in general is more

pronounced about the hair follicles and small superficial blood vessels (fig. 3 *A*) than about the deeper sweat glands. Fibroblasts are slightly increased in number, and in two of the cases there is dilatation of capillaries with swelling of their endothelium.

Spirochetes: A few organisms were found in a focus of polymorphonuclear infiltration in an epithelial peg, also in the epithelial layers of an adjacent hair follicle (table 1, case 4). A few were also seen in foci of edema in dermal papillae and in the subpapillary dermis, particularly about hair follicles. In one other specimen (table 1, case 3) scant, somewhat atypical organisms were present in an area of inflammation just below the epidermis.

(*b*) *Folliculopapules.*—These lesions probably stand midway in evolution between scaly macules and frambesiform lesions, although it is not at all certain that all frambesiomas go through these successive stages. The folliculopapules are characterized by their small size (from 1 to 2 mm.) and by absence of ulceration. They are seen not only during the early phases of the generalized eruption but often when the disease seems to be subsiding. Treponemes have been demonstrated in these lesions by dark field examination in only an occasional instance.

Nine specimens (table 1, cases 6 to 14) are available for microscopic study.

Epidermis: There is no papillary overgrowth of the epithelium, and there is little or no thickening of the epidermis. Edema, with a few polymorphonuclear leukocytes, is seen in only one specimen (case 10). Melanin pigment is not decreased.

Dermis: Scant edema of the dermal papillae and of the subpapillary dermis is present in several of the specimens. A few lymphocytes and plasma cells are present in the edematous areas, in places about sweat glands (figs. 3 C and 5 A), and there is an inflammatory reaction about many of the hair follicles. The endothelial cells of capillaries in the areas of inflammation are somewhat swollen.

Spirochetes: Treponemes are not seen in the epidermis proper, but in one specimen (case 6) scattered organisms are present in the outer layers of epithelial cells of several hair follicles. In this same preparation a moderate number of treponemes are seen in the dermis adjacent to the hair follicles and in small inflammatory foci beneath the epidermis. In two other specimens (cases 10 and 14) a few organisms are found in small areas of edema in the subpapillary zone of the dermis.

(*c*) *Frambesioma.*—Characteristically a frambesiform lesion is a large papule from 0.5 to 2 cm. in diameter, though it may not be more than 0.2 cm. across. The surface is thrown into ridges or convolutions, resembling those of a raspberry, and when not subjected to trauma it is commonly covered by a crust composed of dried serum, epithelial and wandering cells, and bacteria; on removal of the scab, serum laden with treponemes exudes. In figure 1 *C, D* and *E* are shown several frambesiform lesions studied in this series.

Ten specimens of this type of lesion (table 1, cases 15 to 24) are available for microscopic study.

Epidermis: There is moderately increased keratinization of the superficial layers of epithelium. Mitotic figures in the stratum germinativum of the hyperplastic epithelium are increased in number. The rete pegs are elongated, in some cases more than in others (figs. 2 *B* and 5 *C*). Melanin is less conspicuous in the hypertrophic epidermis. Areas of edema are seen in which cells are spread apart with the collection of fluid (fig. 4 *A*), in some places forming small vesicles just beneath the stratum corneum. The number and size of the edematous foci and the

EXPLANATION OF FIGURE 3

A (case 4, table 1), scaly macule of yaws (× 88), showing slight thickening of the epidermis with increased keratinization; there is an inflammatory reaction in the dermis and about a hair follicle. Spirochetes were demonstrated in this case.

B (case 9, table 2), papule of syphilis (× 88), showing edema and also infiltration of lymphocytes in the dermis. Several multinucleated giant cells are present in the deeper part of the lesion. Spirochetes are found in the edematous tissue beneath the epithelium in appropriately prepared sections.

C (case 6, table 1), folliculopapule of yaws (× 88), showing slight edema with infiltration, chiefly of lymphocytes, below the epidermis and around a hair follicle. Spirochetes are found in this area (see fig. 7 *G*).

D (case 32, table 1), late lesion of yaws (× 88), to show downward proliferation of epithelium forming a cystlike space. In this epithelium are numerous spirochetes (see fig. 7 *F*). There are leukocytes in the epithelium and lymphocytes and plasma cells in the corium.

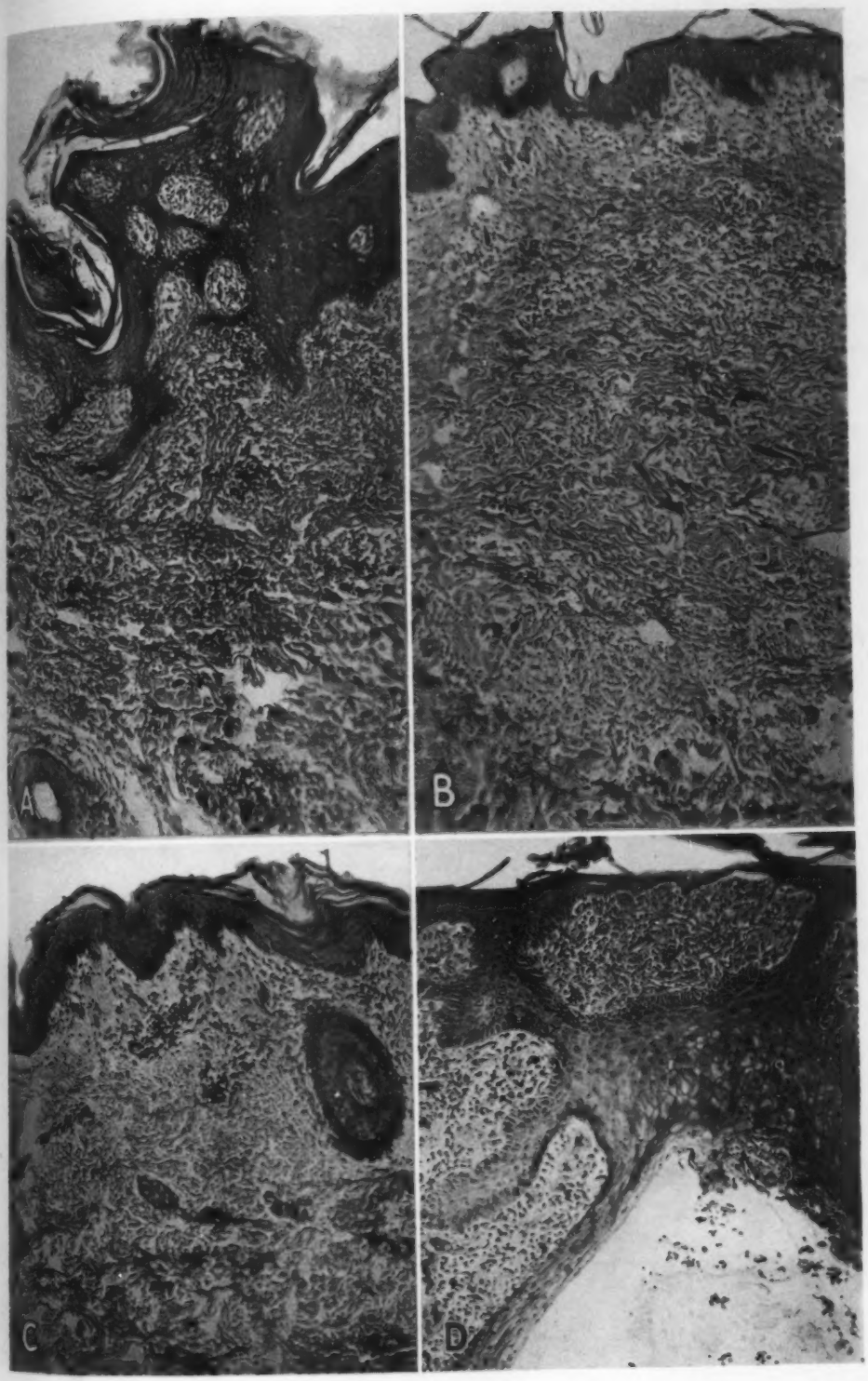


FIGURE 3

EXPLANATION OF FIGURE 4

A (case 24, table 1), frambesiform papule of yaws (× 240), showing dilatation of capillaries and edema of dermal papillae with leukocytes. There are many leukocytes in the epidermis, with formation of small abscesses; there is edema.

B (case 17, table 1), frambesiform papule of yaws (× 240), showing more extensive edema of papillae, with leukocytes in the epithelium and in the adjacent rete pegs. Spirochetes are very numerous in areas such as are shown in figures 4 *A* and *B*.

C (case 17, table 1), frambesiform papule of yaws (× 240), showing infiltration of lymphocytes and plasma cells about capillaries in the subpapillary dermis with slight amount of edema.

D (case 24, table 1), frambesiform papule of yaws (× 240), showing edema and infiltration of lymphocytes and plasma cells about sweat glands.

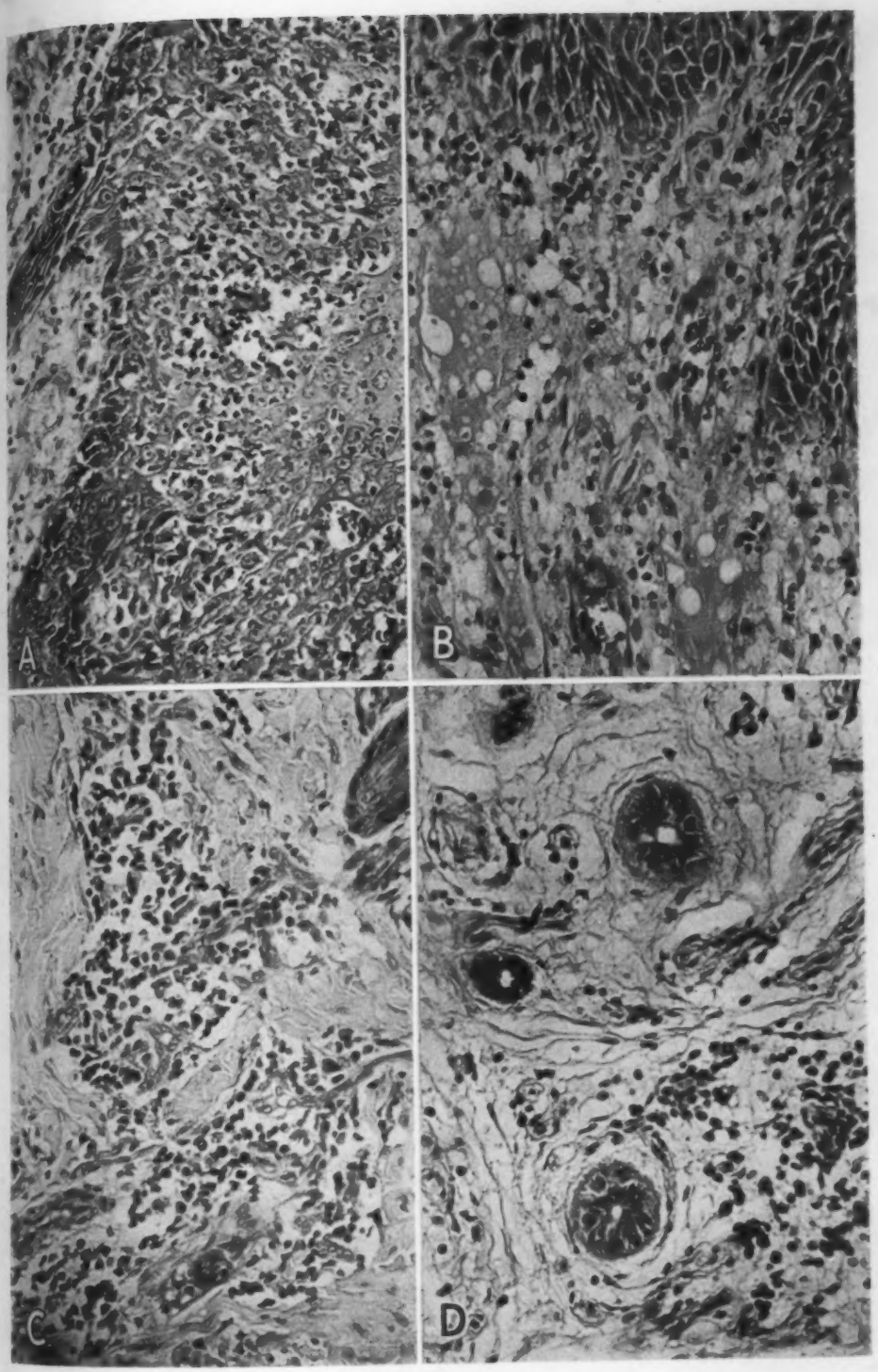
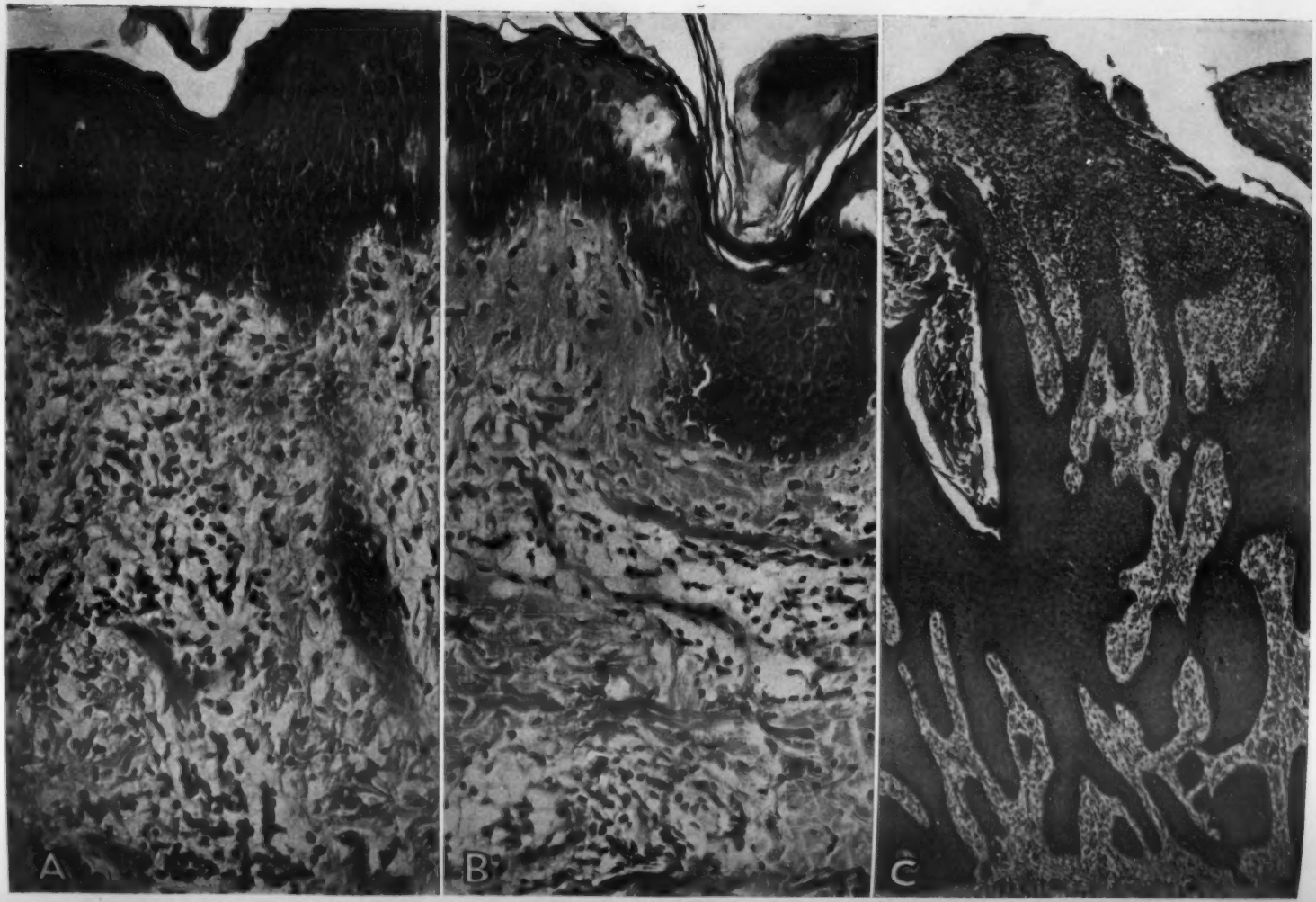


FIGURE 4



EXPLANATION OF FIGURE 5

A (case 10, table 1), folliculopapule of yaws (× 240), showing edema, lymphocytes and a few plasma cells in the dermis. *B* (case 5, table 2),

distribution and extent of the polymorphonuclear leukocytic infiltration vary in the different specimens. Necrosis is found not only in the more superficial part of the epidermis but also to a lesser extent associated with the deeper areas of edema. Leukocytes are very numerous in the superficial layers of the epithelium in some of the specimens and form minute abscesses (fig. 4 *A*). However, foci of edema and leukocytic exudate are seen in the suprapapillary epidermis and rete pegs in places where there is little or no exudate in the outer layers of the epithelium.

Dermis: The papillae of the dermis are swollen by congestion of the blood and lymph vessels and spreading apart of the connective tissue fibrils by the accumulation of fluid (fig. 4 *A* and *B*). Lymphocytes and plasma cells are found in moderate numbers in the papillae, and polymorphonuclear neutrophilic leukocytes are numerous in the tips of papillae adjacent to the areas of maximum inflammation in the epidermis (fig. 4 *B*). Eosinophilic leukocytes are seen in small numbers in almost all of the specimens.

In the subpapillary dermis, there is abundant but variable infiltration by lymphocytes and plasma cells. When this infiltration is least, it is noted particularly about hair follicles, around or adjacent to lymph and blood vessels (fig. 4 *C*) and, in the deep parts of the lesion, about sweat glands (fig. 4 *D*). When it is greatest, there is a zone of closely packed cells beneath the papillae, with less distinct perivascular distribution. Plasma cells are generally two or three times as numerous as lymphocytes. Polymorphonuclear leukocytes are relatively few in this part of the lesion. There is slight proliferation of fibroblasts, and the endothelial cells of the capillaries are somewhat swollen in the inflammatory areas. The walls of medium-sized and larger blood vessels present no appreciable alterations from normal.

Spirochetes: Of the ten specimens studied, one (case 20) was fixed in Zenker's fluid, and preparations for the demonstration of organisms could not be made. In all of the remaining specimens treponemes are seen. They are usually more numerous where the infiltration of leukocytes in the epidermis is most pronounced, usually in zones over the apexes of dermal papillae (fig. 7 *B*). In some cases they are in tremendous numbers, so that two or three hundred may be seen in an oil immersion field, and individual organisms are distinguished with difficulty. In some preparations spirochetes are seen in the more superficial, partly keratinized and partly necrotic epithelium. Occasionally a rete peg may contain organisms even in its deepest extremity. In the dermis, spirochetes are found in considerable numbers in the apexes of papillae adjacent to the areas where they are abundant in the epidermis. Occasionally a few organisms are seen in the deeper parts of the dermal papillae and rarely in the subpapillary zone of inflammation. There is no evidence that any are actually within cells. In fact, they are more commonly observed free in the edematous stroma with no obvious relationship to the cellular elements (fig. 7 *C*). In the areas of acute inflammation, where polymorphonuclears are especially numerous, the spirochetes may be poorly impregnated by the silver and appear much thinner than usual; often they are fragmented, form coils and loops or appear as chains of irregular granules. Dark, well impregnated organisms may be found a short distance away.

(*d*) *Plantar Papules.*—Papules occurring on the palms of the hands differ in no essential respect from frambesiform lesions elsewhere on the body. On the soles, however, the similarity is not readily apparent, for the papule instead of projecting above the level of the sole usually forms the base of a small depression. Its surface, nevertheless, is typically frambesiform, and treponemes are usually present in abundance, so that lesions of this type may be considered the counterpart

EXPLANATION OF FIGURE 5

A, case 10, table 1), folliculitis of yaws (×240), showing edema, lymphocytes and a few plasma cells in the dermis. *B* (case 5, table 2), [illegible] (×240), showing edema, lymphocytes and a few plasma cells in the epithelium. *C* (case 5, table 2), [illegible] (×240), showing edema, lymphocytes and plasma cells in the dermis. *D* (case 5, table 2), [illegible] (×240), showing edema, lymphocytes and plasma cells in the dermis.

of frambesiomas which occur on the palms or other skin surfaces. The epithelial surface eventually undergoes necrosis, giving rise to an ulcerated lesion, which is exceedingly painful on walking.

One specimen (table 1, case 25) is available for microscopic study.

Epidermis: In appearance this lesion is similar to the frambesiform lesions except that the rete pegs are thicker and more irregular in outline and edema is inconspicuous save for hydropic degeneration of a few cells, the nuclei of which have shrunk away from the cytoplasm.

Dermis: In the areas of most intense inflammation there is necrosis of the walls of some of the small vessels. In the subpapillary layer of the dermis are fairly heavy bands of connective tissue, which surround irregular areas of edema, in which are many lymphocytes and plasma cells. Otherwise the structure is like that of a frambesioma.

Spirochetes: Many organisms are present in the epidermis adjacent to the dermal papillae and are especially numerous in foci of polymorphonuclear infiltration. In the dermis the spirochetes are most abundant near the tips of the papillae.

3. *Late Lesions.*—Late lesions can be distinguished clinically from those already described by their appearance and the failure to demonstrate T. pertenue on dark field examination.

(*a*) *Hypertrophic Type.*—These lesions comprise nodules of varying sizes as illustrated in figure 1 *F*. The surface of the lesion is usually not ulcerated, though often cystic degeneration of the center of the lesion occurs. T. pertenue has not been demonstrated in this type of lesion.

Two specimens (table 1, cases 26 and 27) are studied microscopically.

Epidermis: There is much hyperplasia of the epithelium, producing a distinct papillary appearance (fig. 6 *A*). This is due in part to hypertrophy of the rete pegs and in part to thickening of the surface epithelium with an increase of keratinization. There is variation in the size and thickness of the epithelial pegs, several being of considerable width. Melanin in the hypertrophic epithelium is greatly decreased. Small areas of edema, which often contain polymorphonuclear leukocytes, are found in the epidermis of both specimens, more prominent in the deeper layers adjacent to the dermal papillae. Lymphocytes accompany the leukocytes in a few places.

Dermis: Many of the dermal papillae are edematous, and a few polymorphonuclear leukocytes are seen near their tips, adjacent to the foci of similar cells in the epidermis. Lymphocytes and especially plasma cells are more numerous. In the subpapillary part of the dermis edema is conspicuous, and infiltration with lymphocytes and plasma cells is more extensive than in the papillae, cells of the two types being in approximately equal numbers. A few eosinophils are seen here as well as in the papillae. There is less edema about the sweat glands, and the cellular exudate is not as abundant. In a few foci are found epithelioid cells and a very few multinucleated giant cells, but large mononuclear cells are not conspicuous. Some proliferation of fibroblasts and swelling of endothelial cells of capillaries are seen in both the papillary and subpapillary dermis. There are no changes in the small arteries.

Spirochetes: Treponemes are not found in the epidermis or dermis of either of the two specimens.

(*b*) *Destructive Type.*—This type of lesion, which varies in size and conformation, is often indistinguishable from the gumma of syphilis, and differentiation is frequently possible only on the basis of the history or accompanying lesions. The edges are usually somewhat hypertrophic, and the base is covered with sluggish

granulation tissue. The treponemes of yaws cannot be found on dark field examination, although spirochetes of other types are frequently present.

Nine specimens (table 1, cases 28 to 36) are studied microscopically.

Epidermis: As in the hypertrophic lesions described, there are hyperplasia of the rete pegs and increased keratinization of the surface epithelium (fig. 6 *B*). In addition, there is ulceration, which in some instances is manifested by relatively small areas of necrosis, and in others by large excavations, the section being taken from the edge of the crater. Areas of edema in the epidermis are frequently infiltrated by leukocytes. The rete pegs adjacent to the ulcer are often unusually irregular and hypertrophic. Here the melanin pigment, which throughout the hypertrophic epidermis is less than in the normal skin, is almost completely absent.

Dermis: Beneath intact epidermis the inflammatory reaction resembles that in the hypertrophic lesions of late yaws and is accompanied by similar foci of edema and leukocytic infiltration in both papillary and subpapillary zones of the dermis. Groups of mononuclear cells, some of which are epithelioid, are found in several of the preparations. In a few instances these form very distinct tubercles, in which are several multinucleated giant cells, usually with peripherally located nuclei. They are situated in the base of the ulcer or at different depths in the subpapillary dermis. In some places giant cells are seen unassociated with the mononuclear cells.

In the margins of the ulcers necrosis is present in varying amounts with exudation of polymorphonuclear leukocytes. Dense fibrous tissue occurs in the deeper part of many of the lesions, with superficial vascular granulation tissue infiltrated by many leukocytes and lymphocytes and fewer plasma cells. In the dense fibrous tissue are small arteries with thickening of their walls, in some instances obviously due to intimal proliferation. The lumens of some of them are greatly reduced (fig. 6 *C*). In the base of one chronic ulcer (case 34), which persisted twenty years and did not respond to treatment, thickening of small vessels was particularly conspicuous.

Spirochetes: In only two specimens (cases 32 and 31) were spirochetes demonstrated. In one (case 32), a lesion characterized by very irregular extensions of epithelium into the dermis, organisms were found in moderate numbers in this epithelium and in the adjacent connective tissue. In the other specimen only two treponemes were recognized. These were situated in the edge of the ulcer, a short distance beneath the tip of an elongated rete peg.

(*c*) *Subcutaneous Gumma.*—In patients with late cutaneous lesions of the destructive type there occasionally occur subcutaneous nodules which from their location and consistency seem to be closely allied to the lesions of the skin. The skin overlying them may ulcerate, so that it becomes difficult to determine whether they originated in the cutaneous or in the subcutaneous tissue.

Two lesions (table 1, cases 37 and 38) are studied microscopically. They consist of irregular nodules in the subcutaneous fatty tissue. There is considerable difference in the appearance of the two specimens, and they will be described separately.

One (case 38) is composed of dense fibrous tissue which extends as irregular projections into the adjacent fat. This tissue is hyalinized and relatively acellular except for a few areas of proliferation of fibroblasts. Lymphocytes are diffusely scattered through it; there are a few polymorphonuclear leukocytes and an occasional eosinophil. A few small arteries are surrounded by cuffs of lymphocytes. Small collections of large multinucleated giant cells are seen. Associated with them in some instances are large mononuclear cells, not distinctly epithelioid. In places, small capillaries with swollen endothelial cells are numerous. This specimen is from the same patient as the late destructive lesion (table 1, case 33).

EXPLANATION OF FIGURE 6

A (case 26, table 1), late hypertrophic lesion of yaws (× 54), showing hyperplasia of rete pegs and extensive infiltration of lymphocytes and plasma cells. There are edema and exudate about sweat glands.

B (case 36, table 1), late destructive lesion of yaws (× 54), showing necrosis of the floor of the ulcer and an inflammatory reaction beneath, involving the adjacent papillae. There is hyperplasia of the adjacent rete pegs.

C (case 36, table 1), late destructive lesion of yaws (× 48), showing thickening of the walls of small arteries in the base of the ulcer near the subcutaneous tissue. The intima of the largest vessel is hyperplastic. There is infiltration of the perivascular tissue by lymphocytes.

D (case 3, table 3), juxta-articular nodule of yaws (× 88), showing dense fibrous tissue and infiltration of lymphocytes and large mononuclear cells containing lipoid.

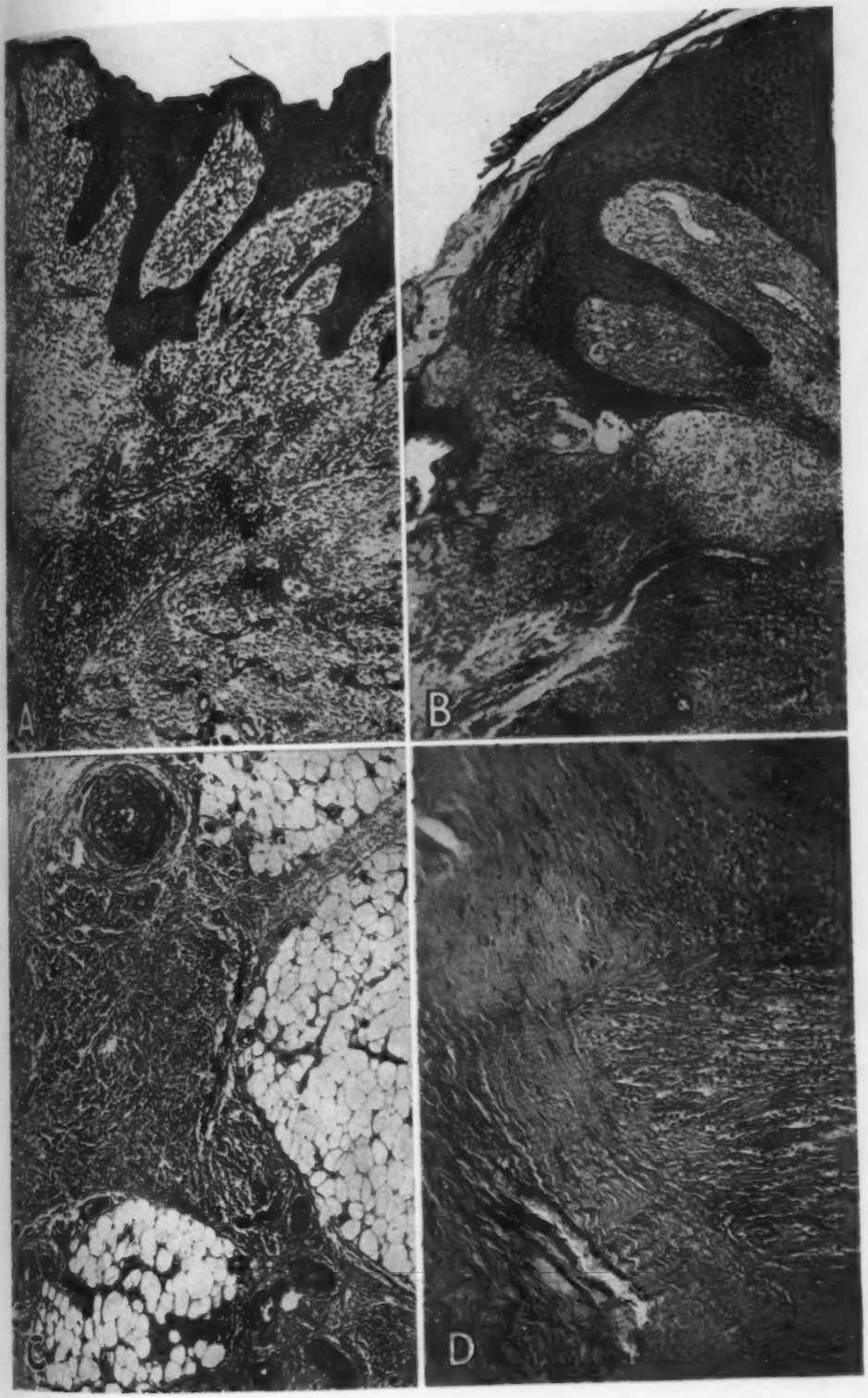


FIGURE 6

EXPLANATION OF FIGURE 7

Spirochetes in yaws and syphilis. Silver impregnation by the Warthin-Starry method. Sections *A* (case 1, table 1), *D* (case 24, table 1) and *E* (case 15, table 1) were toned with silver chloride and counterstained with hematoxylin and eosin. All were taken at a magnification of 1,800, with oil immersion.

A (case 1, table 1), initial lesion of yaws, showing spirochetes in the epidermis and in the edge of a papilla of the dermis. Leukocytes may be seen in the dermis.

B (case 17, table 1), frambesiform papule of yaws, showing spirochetes in the epidermis, with polymorphonuclear leukocytes.

C (case 17, table 1), frambesiform papule of yaws, showing spirochetes in an edematous dermal papilla, with the epidermis above. There are many organisms in this field, of which only a few are in focus.

D (case 24, table 1), frambesiform papule of yaws, showing spirochetes in a dermal papilla.

E (case 15, table 1), frambesiform papule of yaws, showing spirochetes in a dermal papilla, with polymorphonuclear leukocytes.

F (case 32, table 1), late destructive lesion of yaws, showing spirochetes in an irregular downgrowth of the epidermis (fig. 3 *D*).

G (case 6, table 1), folliculopapule of yaws, showing spirochetes in the dermis next to a hair follicle.

H (case 9, table 2), secondary papule of syphilis, showing a spirochete in a hair follicle.

I (case 4, table 3), juxta-articular nodule of syphilis, showing spirochetes in dense fibrous tissue.

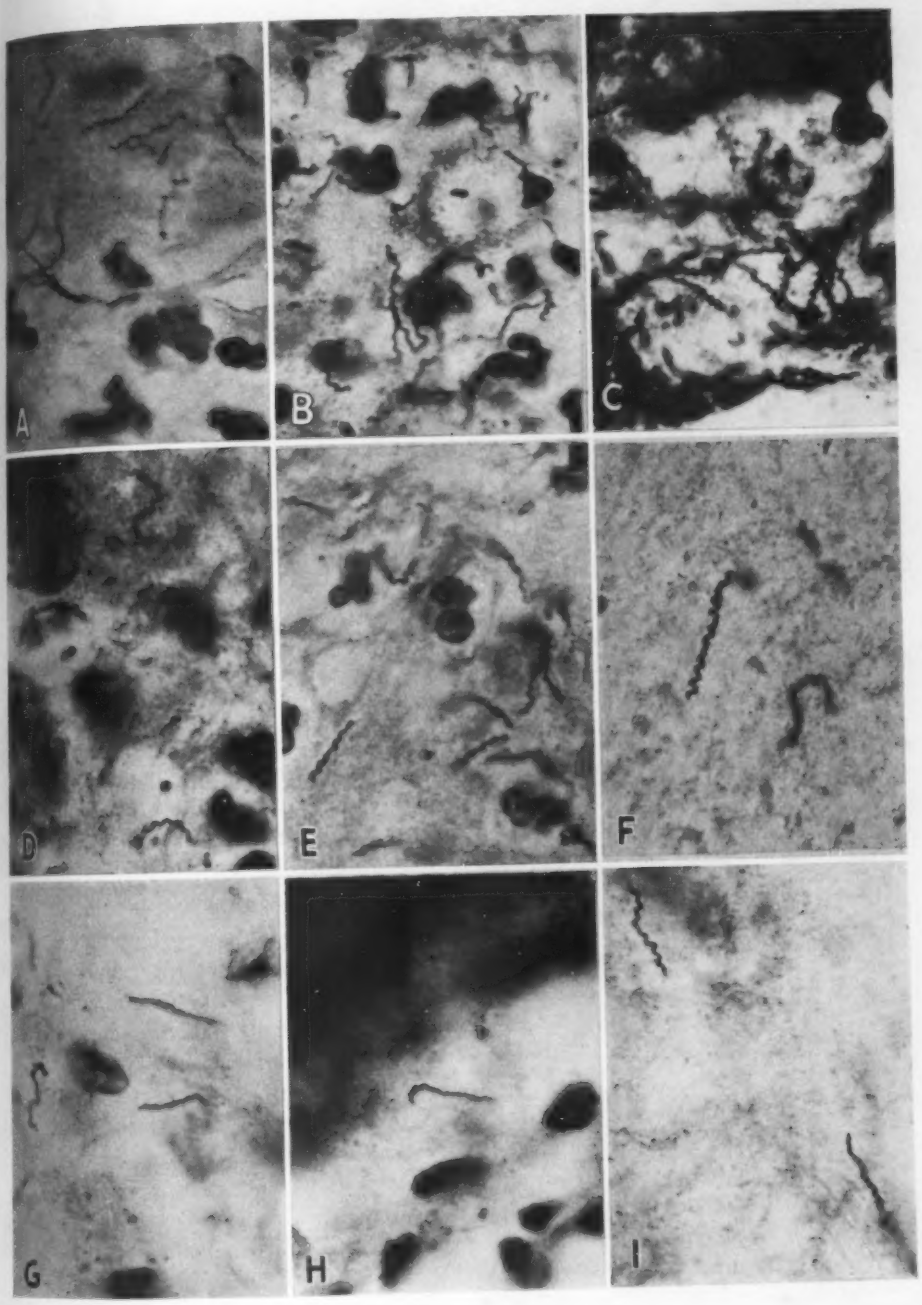


FIGURE 7

The other specimen (case 37) also contains dense fibrous tissue, but there is a much denser infiltration of lymphocytes with numerous eosinophils. In addition, there is a large area of necrosis resembling that of a gumma. In it may be seen nuclear débris and the shadowy outlines of small necrosed blood vessels, in the walls of which remain a few fine fragments of elastic fibrils. Partially surrounding this area of necrosis is an irregular zone composed of mononuclear cells, some of which are elongated while others are polyhedral. The nuclei are usually vesicular and pale and the cytoplasm inconspicuous or moderate in amount and light pink. In places these cells are radially arranged and extend a slight distance into the necrotic tissue. In other places they form distinct tubercle-like structures, which contain multinucleated giant cells. There is no necrosis in these tubercles. Proliferation of fibroblasts is not as prominent as in the first specimen.

Spirochetes: No organisms are seen in either specimen.

SUMMARY OF HISTOLOGY OF YAWS

It is obvious from the preceding descriptions of cutaneous and subcutaneous lesions of yaws that they may be conveniently divided into several distinct morphologic groups. The first group is that in which an overgrowth of the epidermis is the conspicuous feature (compare fig. 2 *A* and *B* and fig. 5 *C*). Two types of lesions may be included: the primary ("initial" or "mother") yaw and the frambesiform lesion. The initial lesion and the frambesiform yaw may be indistinguishable except that fibrous tissue tends to be more abundant with increased age of the mother yaw. Spirochetes are uniformly present in the frambesiform papules. In the initial lesion (table 1, case 2), which was apparently of the greater age, none was seen in sections, though they were seen in dark field preparations (table 1). Organisms were abundant in the other specimen (table 1, case 1). Williams [8] noted the great similarity between the primary lesion of yaws and the frambesioma. Spirochetes were not numerous in the initial lesion which he studied.

The second main group of lesions from an anatomic standpoint is that which is characterized by only slight if any evidence of epithelial hyperplasia. These lesions are the scaly or squamous lesions, some of which are described as annular or ringworm in type, and the folliculopapules. In the folliculopapules there is practically no evidence of hyperplasia of the epithelium and little or no keratinization. The scaly macules present thickening of the epidermis, with some increase of keratinization, and a slight tendency toward hypertrophy of the rete pegs, in which melanin may be somewhat decreased. The changes in the dermis are essentially similar to those in the folliculopapules except that histiocytes (epithelioid cells) may be present in small groups. In both the folliculopapules and the scaly macules, spirochetes are demonstrable in about 50 per cent of the cases. They are more abundant in the dermis, though nowhere in as large numbers as in the frambesi-

8. Williams, H. U.: Arch. Path. **20**:596, 1935.

form lesions. There is but scant literature on the histology of these lesions. MacLeod [9] described and illustrated them. His observations are in close accord with ours.

A third type of lesion is seen late in the disease. It is characterized by necrosis and ulceration with granulation tissue and dense fibrous tissue. There are frequently epithelioid cells or giant cells. In some instances the late lesions may be hypertrophic with little or no ulceration. In these the proliferating epithelial pegs do not, as a rule, extend as deep into the underlying dermis as in the frambesioma and tend to be more irregular in size and shape. Epithelial hyperplasia at the margins of ulcers may be secondary regeneration associated with the chronic inflammation rather than primary hyperplasia. Hallenberger [10] also noted this epithelial proliferation at the edges of the "gummatous" ulcers of yaws. There is in general the same type of exudate in the epidermis and dermis as is seen in the early proliferative lesions, and indeed some of the late hypertrophic lesions may closely simulate the frambesiomas except for the absence of spirochetes.

The fourth type of lesion is the indurated nodule which is found in the subcutaneous tissue. In one instance (table 1, case 38) it consists of dense hyalinized connective tissue, which may represent a healed gumma. It is noteworthy that a late destructive lesion (table 1, case 33) is also present in this case. It is possible that a necrotic nodule (table 1, case 37) may ulcerate through the skin, producing there a destructive lesion.

OCCURRENCE OF SPIROCHETES AND BACTERIA IN YAWS

Noteworthy is the distribution of spirochetes in the different lesions. Their presence in large numbers in the hyperplastic epithelium of the frambesiform lesions of yaws is characteristic and described by most authors. Of more significance is their occurrence in abundance in the dermis. Goodpasture [11] noted them in the tips of the dermal papillae in small numbers, but other observers have found the organisms only in the epithelium, and for that reason have described T. pertenue as being epidermitrophic. It is significant, however, that we have not observed the organisms in the epidermis, including the hair follicles, unless they were also present in the dermis. This is true of the folliculopapules and scaly macular lesions as well as of the frambesiform papules. The almost uniform absence of the organisms in the late lesions confirms clinical observations with dark field examinations. Of particular note is the lack of phagocytosis of the spirochetes by any type of wandering or fixed tissue cell and indeed the entire absence of any evidence that

9. MacLeod, J. M. H.: Brit. M. J. **2**:797, 1901.
10. Hallenberger: Arch. f. Schiffs- u. Tropen-Hyg. (supp.) **20**:5, 1916.
11. Goodpasture, E. W.: Philippine J. Sc. **22**:263, 1923.

the organisms are situated within any cell even in the epidermis, where they are so numerous. Williams [8] studied a number of secondary papillomas of yaws prepared by the Levaditi method and found it difficult to say whether or not the organisms occurred within cells. The almost complete absence of macrophages in the initial lesions and frambesiomas in our cases is noteworthy.

The possible rôle played by secondary invaders, either bacterial or spirochetal, in influencing the structure or the course of the lesions has been considered by several authors. Castellani [12] stated that fungoid ulcerations are invaded quickly by all sorts of organisms, and, besides innumerable bacteria, often spirochetes of various kinds are present. In the earlier stages, when the eruptions of the skin are covered by intact epithelium, no bacteria are found either on smear or culture, but rare spirochetes may be observed. Unna [13] believed that the polymorphonuclear leukocytes were the result of secondary infection. In his recent review of yaws Williams [8] said, "It can hardly be doubted that secondary infection plays an important part in many cases of yaws, but evidence is lacking to show how much the microscopic picture is modified by secondary infection."

In the hope of throwing some light on this problem we have prepared sections from representative lesions of yaws and syphilis according to MacCallum's [14] method for demonstrating bacteria. In one specimen of a late lesion of yaws with deep ulceration a number of large bacilli, morphologically compatible with fusiform bacilli, were seen in the superficial necrosis. In other lesions, cocci were present in scant numbers in the keratinized surface epithelium in a few instances, while more usually no such micro-organisms were demonstrated. In the areas in both epidermis and dermis in which polymorphonuclear leukocytes were abundant, bacteria were absent. Absence of bacteria and the occurrence of foci of leukocytes with scant if any destruction of the overlying epidermis are strong evidence that the spirochetes alone are responsible for the inflammatory reaction. It is noteworthy that the spirochetes are abundant in the areas of polymorphonuclear exudate, particularly in those situated in epidermis in contact with the tips of dermal papillae, and in the tips of these papillae.

In one case frambesiform lesions were excised before and one week after the first treatment with arsphenamine. It is significant that the spirochetes present in large numbers before treatment disappeared, and

12. Castellani, A.: J. Trop. Med. **9**:1, 1906.

13. Unna, P. G.: Die Histopathologie der Hautkrankheiten, in Orth, J.: Lehrbuch der specialen pathologischen Anatomie, Berlin, A. Hirschwald, 1894, p. 506.

14. MacCallum, W. G.: The Pathology of the Pneumonia in the United States Army Camps During the Winter of 1917-1918, Monograph 10, Rockefeller Institute for Medical Research, 1919, p. 47.

the epithelial hyperplasia and infiltration of leukocytes were remarkably decreased. No bacteria could be identified in sections taken either before or after treatment. If the original lesion had been in part the result of secondary infection, no such dramatic response to arsenicals could have been expected. A similar rapid change in the histologic structure following treatment was described by Goodpasture,[11] who found that within forty hours after a therapeutic dose of neoarsphenamine all treponemes demonstrable by Levaditi's method had disappeared from an early lesion of yaws. He thought it probable that neoarsphenamine destroyed polymorphonuclear leukocytes and that their destruction favored rapid disintegration of treponemes. We have observed that where leukocytes are very numerous the spirochetes frequently are poorly stained and granular in appearance, as described before. Williams [8] also noted this disintegration of the organisms.

We have attempted to compare, when possible, the incidence of spirochetes as demonstrated in sections of the various lesions of yaws with the Wassermann titration. As may be seen by consulting table 1, there is no direct correlation. In some instances a high titer is associated with failure to demonstrate the organisms, while in other cases a low titer is present when spirochetes are numerous. However, it is generally true that there is a higher incidence of spirochetes in the lesions removed at the height of the clinical disease than in those removed during the earlier or later stages. The microscopic appearance of lesions with similar gross characteristics is the same, no matter whether they occur early or late in the disease.

Eosinophil leukocytosis in association with yaws was noted by Castellani,[12] who suggested that it was referable to the presence of intestinal worms, because the patients' stools frequently contained ova of Ascaris lumbricoides and other parasites. Williams [8] noted eosinophils in the lesions. We have also found them in small numbers in seven of ten frambesiform papules and seven of eleven late hypertrophic and destructive lesions. Their more frequent occurrence in the papillary lesions is probably the result of more active exudation of cells of all types rather than evidence of allergic response.

HISTOLOGIC OBSERVATIONS ON CUTANEOUS LESIONS OF SYPHILIS

1. *Primary Lesions.*—No material from Jamaica is available for examination.

2. *Secondary Lesions.*—The cutaneous lesions of secondary syphilis among the natives of Jamaica differ in no essential respects from those encountered among persons living elsewhere. Macular, papular and pustular lesions may occur alone or together. Not only did every patient included in this study present typical lesions of secondary syphilis but with one exception the history of the case and the circumstances under which the disease was acquired permitted of a clear differentiation from yaws. In one case (13, table 2) the patient resided in an area

where yaws was endemic, there was no history or physical evidence of a primary lesion of syphilis or yaws, and the diagnosis rested on the character of the cutaneous eruption alone. Among the other patients, however, four of eight males exhibited either a penile chancre or the indurated scar of a recent chancre. Acute iritis occurred in five patients, mucous patches of the lips or vulva in three, and acute (syphilitic) meningitis in one, all of which are lesions encountered rarely if ever in yaws. Of the thirteen patients, the secondary rash was maculopapular in four and papular in nine, although these lesions were not identical in appearance with those of yaws to which similar names have been applied. The maculopapular lesions resembled, in gross appearance, the rash of measles more than the scaly macular eruption noted in yaws. Likewise, the syphilitic papules were not so elevated, the base was broader, and there was less evidence of hyperkeratinization of the surface than is encountered in comparable lesions of yaws.

These lesions (with one exception which will be described separately) are inconspicuously elevated. There is in general little histologic difference between the maculopapules and the papules. Thirteen are studied microscopically.

Epidermis: There is scant proliferation of the epithelium, though in some lesions, in places, slight elongation of rete pegs with slight thickening of the overlying epidermis is noted. Foci of edema are seldom present in the epithelium, and there are few inflammatory cells. Pigment is somewhat decreased in the areas of slight hyperplasia.

Dermis: Edema of dermal papillae is present but scant in most of the specimens, with small numbers of lymphocytes and plasma cells. In the subpapillary dermis in all the specimens are areas of edema (figs. 3 *B* and 5 *B*), frequently about hair follicles and occasionally about the sweat glands, with lymphocytes and plasma cells. There are occasional eosinophils. In seven of the specimens are seen small collections of mononuclear cells resembling epithelioid cells, in some instances forming fairly well defined tubercles. Necrosis of these structures occurs rarely. In five specimens there are multinucleated giant cells (fig. 3 *B*). Fibroblasts are slightly increased in number in the inflammatory foci. The endothelium of capillaries is somewhat swollen, but larger blood vessels show no changes.

One case (13, table 2) was characterized by papular lesions. Microscopically the specimens present prominent hyperplasia of the epithelium with elongated rete pegs. There are edema and exudate of polymorphonuclear leukocytes in the epidermis and in the tips of the dermal papillae. Plasma cells and lymphocytes are numerous in the dermis. The lesion resembles the frambesioma of yaws.

Spirochetes: A few organisms are found in the epidermis of two specimens, in one instance in the superficial layers of a hair follicle (fig. 7 *H*) and in the other in a downfold of epithelium, also probably part of a hair follicle. In these two specimens (table 2, cases 3 and 8) treponemes are also found among lymphocytes and plasma cells adjacent to the hair follicles. In six other specimens they are seen in edematous areas of the dermis below the epidermis or adjacent to hair follicles. None is found in the dermal papillae except in one (case 13, table 2), in which the organisms are very numerous in the epithelium and in tips of papillae of the dermis. Spirochetes are not seen in epithelioid cells, giant cells or other cells. It is noteworthy that spirochetes were present in eight of the nine lesions clinically diagnosed as papules, while they were seen in only one of the four maculopapules.

3. *Tertiary Lesions.*—The only specimen of this category available for study was obtained from a patient with precocious tertiary syphilis. The lesions are circular in configuration, destructive in type, crusted and show no treponemes on

dark field examination. Since the disease in this patient was of only two years' duration the lesions are directly comparable with the late lesions of yaws which occur within the first few years after infection.

The following are the microscopic observations:

Epidermis: The section is from the edge of an ulcer. For some distance adjacent to its margin there is slight hyperplasia of the epidermis, characterized chiefly by increased length and width of the rete pegs. The epithelium above the pegs is also slightly thickened. There is a moderate amount of keratin. In the epidermis remaining on the specimen there is no edema or cellular infiltration. Melanin is not decreased in amount.

Dermis: Beneath the intact epithelium are small numbers of lymphocytes with a slight amount of edema about small blood vessels. Plasma cells are rare. There is edema but very scant infiltration of cells about the sweat glands. In the tissue beneath or adjacent to the ulcer are very numerous lymphocytes about the sweat glands and a few polymorphonuclear leukocytes. Along one edge of the ulcer there is necrotic tissue containing many leukocytes. Some swelling of the endothelium of capillaries is seen but no conspicuous changes in the medium-sized or smaller arteries. Eosinophils are rare. Epithelioid cells or giant cells are not observed.

Spirochetes: None is seen.

JUXTA-ARTICULAR NODULES

Subcutaneous nodules in proximity to joints occur in both yaws and syphilis, but similar nodules may have other etiology. The nodules are ordinarily smooth, rounded, quite firm or even stony hard, painless and movable beneath the skin. They occur most often near the elbow, knee and hip joints in the order named. The extensive literature on the subject has been adequately reviewed by Hopkins,[15] Strong and Shattuck[16] and Jessner.[17] Although we have had the opportunity of studying juxta-articular nodules in only five cases, several points of interest are presented. In three of the cases the diagnosis of yaws was fairly clearly established, while in the other two there was no definite history of yaws, and it was impossible to exclude syphilis as the etiologic factor. The Wassermann reaction was positive in all but one. Pertinent data on these instances are given in table 3. Particularly noteworthy are the following points: In case 1 the nodules occurred simultaneously with infectious lesions of the skin not more than two years after yaws was acquired. No treponemes were demonstrated in the nodules by dark field examination or on inoculation in animals. In

15. Hopkins, H. H.: Bull. Johns Hopkins Hosp. **49**:5, 1931.

16. Strong, R. P., and Shattuck, G. C.: The African Republic of Liberia and the Belgian Congo, Based on the Observations Made and Material Collected During the Harvard Expedition, 1926-1927, Cambridge, Harvard University Press, 1930, vol. 1, pt. 2, pp. 258-271.

17. Jessner, M.: Arch. f. Dermat. u. Syph. **152**:132, 1926.

case 2 the Wassermann reaction of the blood was negative. In case 3 the capsule of the nodule was tough and fibrous, but the center was filled with a seropurulent fluid. Cholesterol crystals were abundant in the capsule.

Yaws.—The microscopic observations on three specimens (table 3, cases 1, 2 and 3) of this lesion are as follows: In two of the specimens the changes are similar: There is dense fibrous tissue, containing relatively few cells. Lymphocytes and plasma cells or lymphocytes alone are present in varying numbers about blood vessels. It is noteworthy that one of these lesions occurred two years, the other sixteen years, after infection. The third specimen (case 3) consists for the most part of dense hyalinized connective tissue, in which there are groups of spindle-shaped spaces which have evidently contained cholesterol crystals. There are groups of large mononuclear cells with vacuolated cytoplasm. The blood vessels at the periphery of the hyaline tissue do not present noteworthy changes.

TABLE 3.—*Data on Juxta-Articular Nodules*

Case	Race of Patient	Age, Yrs.	Sex	Diagnosis	Estimated Duration of Infection	Associated Lesions	Location of Nodules	Approximate Diameter of Largest Nodule	Wassermann Test	Spirochetes Found in Stained Section
1	Black	11	F	Yaws	2 yrs.	Frambesiform, infectious plantar	Both elbows	8 mm.	Positive	None
2	Black	22	F	Yaws	16 yrs.	Plantar hyperkeratosis	Left knee	2 cm.	Negative	None
3	Black	57	F	Yaws	27 yrs.	None	Both elbows	2 cm.	Positive	None
4	Black	29	M	Probably syphilis		None	Left elbow	2.5 cm.	Positive	Moderate number
5	Brown	23	F	Probably syphilis		None	Both elbows	1 cm.	Positive	Few

Spirochetes: One specimen (case 1) was fixed in Zenker's solution, so that stains for the organisms could not be made. In the other two no treponemes were demonstrated.

Probably Syphilis.—Two specimens are available for microscopic examination. They consist of dense, partly hyalinized fibrous tissue with some areas in which fibroblasts are numerous. There are accumulations of lymphocytes and plasma cells, which in one specimen are frequently, and in the other are predominately, perivascular in distribution. Among the fibroblasts in one instance are many eosinophils. In the other there are small areas of edema and necrosis with polymorphonuclear leukocytes.

Spirochetes: Treponemes are found in both the specimens. They are situated in areas where polymorphonuclear leukocytes have accumulated and elsewhere in places in which connective tissue is dense (fig. 7*I*). Indeed they are perhaps more numerous in the denser tissue.

With the exception of one specimen from a patient (case 3) with yaws, in which there are cholesterol crystals and xanthoma-like cells as described by Strong and Shattuck,[16] the juxta-articular nodules are all essentially similar in histologic

appearance, consisting of dense fibrous tissue with, as a rule, scant cellular infiltration. Hopkins [15] described from Baltimore two cases in which xanthoma cells were found in juxta-articular nodules. One of the patients had a positive Wassermann reaction of the blood, and a remaining nodule disappeared under antisyphilitic treatment. He was unable to demonstrate spirochetes by silver impregnation in the four syphilitic nodules in which search for them was made. It is noteworthy, however, that while spirochetes were demonstrated in none of the juxta-articular nodules from cases of yaws which we studied, they were seen in the two which were believed to be syphilitic in origin. Jessner [17] stated that the histology of juxta-articular nodules of yaws and syphilis is practically the same and that the one possible difference is the failure to demonstrate spirochetes in the nodules of syphilis, while they have been found in those of yaws. Spirochetes have been demonstrated on a few occasions in juxta-articular nodules by Van Dijke, Sobernheim, Clapier and Van Hoof,[18] but there may be some doubt as to whether the lesions were due to yaws or to syphilis.

COMPARISON OF LESIONS OF YAWS AND SYPHILIS

The difficulties of obtaining comparable lesions of the two diseases are considerable. However, we have here attempted to make a comparison on the basis of the age and anatomic characteristics of the lesions.

Primary lesions of syphilis were not obtained from Jamaican patients, so that no comparison can be made between the initial lesions of the two diseases as they occur in that country. It is obvious from descriptions of chancres recorded in the literature on the subject, as well as from our own experience, that there are certain differences in the initial lesions of yaws and syphilis. According to Strong and Shattuck,[16] the chancre begins as a papule which almost from the beginning exhibits erosion of the surface epithelium. The underlying tissue becomes thickened and indurated because of the great accumulation of cells in the skin and subcutaneous tissue. The spirochetes of syphilis are found chiefly between the epithelial cells in the epidermis but also in the connective tissue between the fibrils and in the adventitia and more rarely in the intima of blood vessels. Other authors, as Ehrman [19] and Fordyce,[20] have described epithelial hyperplasia in chancres. Auspitz and Unna [19] stated that with syphilitic ulceration there is hypertrophy of the epithelium with deep branches. Fordyce [20] found some acanthosis in sections from the edge of a fully developed chancre, the epithelial pegs being more widened than lengthened. He expressed the opinion that atrophy, hypertrophy, erosion and ulceration of the epithelium are all secondary to inflammatory changes. Perivascular lymphocytic and plasma cell infiltration are described by all observers. Polymorphonuclear leukocytes and occasional eosinophils are described by Strong and Shattuck.[16]

18. Cited by Strong and Shattuck.[16]
19. Cited by Herxheimer.[22]
20. Fordyce, J. A.: J. A. M. A. **49**:462, 1907.

Giant cells were observed by Unna,[19] while Neumann [21] and Fordyce [20] did not find them. Vascular changes were stressed by Fordyce,[20] Herxheimer,[22] von Biesiadecki, Auspitz and Unna, Wredensky and Rieder.[19] They stated that swelling and proliferation of the endothelial cells of capillaries and larger blood vessels are a prominent feature and often lead to obliteration of the lumens. All of the coats may undergo proliferation, particularly in the later stages of the lesion.

In contrast the epithelial hyperplasia of the initial lesion of yaws, with elongation of the papillae, is a prominent feature and occurs irrespective of the presence of necrosis. The obliterative changes in the vessels are not seen in the initial lesion of yaws as they are in the chancre, though there may be swelling of the endothelium of capillaries. Perivascular infiltrations of lymphocytes and plasma cells are seen, though Williams [8] held that the changes in and around the blood vessels are less pronounced than in chancres. He found spirochetes in areas of leukocytic exudate in the epithelium. We found them in both epidermis and dermis in one case.

Of the secondary lesions of yaws, the frambesiform papule is usually considered to have a characteristic histologic picture. With the exception of case 13, table 2, the etiology of which may not be certain, we have no syphilitic lesion to compare with it. In this case the microscopic structure, with prominent hyperplasia of the epidermis and leukocytic infiltration, and the distribution of the spirochetes were identical with what is seen in the frambesioma. McCarthy [23] described extensive epidermal hyperplasia in certain secondary lesions of syphilis which he termed frambesiform syphilids and believed may be indistinguishable from secondary frambesiform lesions of yaws. Fordyce [20] said that in the larger papular syphilids there are parakeratosis, acanthosis and edema, with extensive invasion by polymorphonuclear leukocytes. The papule is produced chiefly by the epithelial hyperplasia. In the condyloma,[24] he ascribed the great papillomatous development to excess moisture. According to MacLeod,[9] the epithelial hyperplasia in yaws is equaled in syphilis only by the condyloma. Dennie [25] described, in a condyloma, hyperplasia of epithelial pegs with leukocytic infiltration of the epithelium and the adjacent tips of dermal papillae. Lymphocytes and plasma cells were found in the dermis. The larger vessels showed no changes except perivascular collars of lymphocytes. He found no spirochetes among the plasma cells or lymphocytes but found a mesh-

21. Neumann, Isidor: Vrtljschr. f. Dermat. **12**:209, 1885.

22. Herxheimer, G.: Ergebn. d. allg. Path. u. path. Anat. **11**:1, 1906.

23. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931, p. 308.

24. Fordyce, J. A.: J. Cutan. Dis. **33**:802, 1915.

25. Dennie, C. C.: J. Cutan. Dis. **33**:507, 1915.

work of the organisms among the epithelial cells of the rete pegs. The only part of the dermis involved by them was the tips of the dermal papillae. Dennie's observations are very similar to those which we have made in the frambesiomas.

In our series the folliculopapules and squamous lesions of yaws are comparable with the maculopapules and papules of syphilis, of which we have an adequate representation in our material. In neither of these groups is there prominent hyperplasia of the epidermis. Some elevation of the gross lesions is produced by edema and exudate in the dermis, frequently about hair follicles, in both yaws and syphilis. The edema and exudation of lymphocytes and plasma cells are perivascular in both diseases, occurring about the small capillaries, chiefly in the subpapillary dermis. Lymphocytes somewhat outnumber the plasma cells. There is slight if any difference in the degree of inflammation about sweat glands. There is swelling of the capillary endothelium in both yaws and syphilis, but in these lesions there are no conspicuous changes in the arteries. Proliferation of fibroblasts is not more prominent in one than in the other. The incidence of giant cells varies in the two diseases. We have not seen them in the folliculopapules of yaws, but in two of the three scaly lesions there are epithelioid cells with a few multinucleated giant cells. In the maculopapular and papular lesions of syphilis these cells are more numerous, and in seven of thirteen specimens there are epithelioid cells, and in five of these, multinucleated giant cells. This difference in the occurrence of epithelioid cells and giant cells is probably not constant enough to form a basis for differential diagnosis. The absence or infrequent occurrence of giant cells in yaws has been reported by Strong and Shattuck,[16] MacLeod,[9] Castellani[12] and White and Tyzzer.[26] Spirochetes are found slightly more often in the maculopapules and papules of syphilis (nine of thirteen) than in the folliculopapules and scaly lesions of yaws (five of eleven). There is no essential difference in the distribution of the organisms in the comparable lesions of the two diseases.

We have only one tertiary cutaneous lesion of syphilis available. Spirochetes are not demonstrated. This lesion is not unlike some of the late ulcerative lesions of yaws. Absence of caseous necrosis was believed by Hallenberger[10] to be characteristic of the gummatous lesions of yaws, but we have found necrosis in one subcutaneous nodule of that disease.

The depth of the cellular infiltrations in the lesions of syphilis as compared with those of yaws has been stressed as a differential point. Nevertheless, we have seen inflammatory reaction about the deep sweat glands and hair follicles in yaws (fig. 4*D*) as well as in syphilis. A similar observation has been made by White and Tyzzer.[26]

26. White, C. J., and Tyzzer, E. E.: J. Cutan. Dis. **29**:138, 1911.

The statement has been made (Hallenberger,[10] Marshall [27]) that in the lesions of yaws there are many more plasma cells than in those of syphilis, but White and Tyzzer [26] found that all the cells in the verrucous lesions in one case of yaws which they studied were lymphocytes. We have found that in both the folliculopapules of yaws and the small papules or maculopapules of syphilis plasma cells may be less numerous than lymphocytes. Even in the frambesiform lesions they may vary considerably in number. Absence or infrequency of perivascular distribution of cells has been described in yaws by Strong, Shattuck and Wheeler [28] and MacLeod.[9] On the contrary, in the lesions which we have studied perivascular accumulation of cells has been a prominent feature, best seen where the inflammatory reaction is not intense (fig. 4 *C*).

Most observers except Goodpasture [11] have claimed that spirochetes in yaws are entirely epidermal in situation. This has not been true in the specimens we have studied (fig. 7 *A*, *C*, *D*, *E*, and *G*). Schüffner [29] stated that the organisms are not seen along the vessels (perithelial) as in syphilis, but we have seen them there. We can determine no morphologic differences between S. pallida and T. pertenue in tissues prepared by silver impregnation.

Finally, the histologic feature which has been stressed as characteristic of syphilis is sclerosis with endothelial hyperplasia of blood vessels. Hallenberger [10] said that it could be used for diagnosis of syphilis, because it occurs in all stages in similar typical form. Manson-Bahr,[30] Castellani,[12] Marshall [27] and MacLeod [9] have mentioned the absence or infrequency of these vascular changes in yaws. Nevertheless, if we accepted this criterion we should discard all of our secondary syphilitic lesions because they do not fulfil this requirement. On the other hand, all of our late ulcerative lesions of yaws would be diagnosed as syphilis because some degree of vascular change was present in all (fig. 6 *C*). Strong and Shattuck,[31] however, admitted that all syphilitic lesions do not show typical modification of blood vessels, and, especially in the tertiary stages, syphilitic lesions cannot be distinguished from those of yaws by their histologic appearance.

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27. Marshall, H. T.: Philippine J. Sc. **2**:469, 1907.

28. Strong, R. P.; Shattuck, G. C., and Wheeler, R. E.: Medical Report of the Hamilton Rice Seventh Expedition to the Amazon, in Conjunction with the Department of Tropical Medicine of Harvard University, 1924-1925, Cambridge, Harvard University Press, 1926, p. 40.

29. Schüffner, W.: München. med. Wchnschr. **54**:1364, 1907.

30. Manson-Bahr, P. H.: Manson's Tropical Diseases, revised, ed. 10, Baltimore, William Wood & Company, 1936, p. 576.

31. Strong and Shattuck,[16] p. 272.

CONCLUSIONS

The initial lesion and the frambesiomas of yaws are characterized by epithelial hyperplasia with exudation of polymorphonuclear leukocytes. There are many lymphocytes and plasma cells in the dermis. The scaly macules and folliculopapules have little proliferation of epithelium and only scant infiltrations of lymphocytes and plasma cells in the dermis. In the late lesions of yaws there is usually ulceration with varying degrees of epithelial hyperplasia.

With silver preparation, the treponemes of yaws (T. pertenue) are constantly found in large numbers in the epidermis and more superficial dermis of the frambesiform lesions and may be numerous in the initial lesion. They are demonstrated in small numbers in the hair follicles and dermis of about 50 per cent of the folliculopapules and scaly macules of yaws. They are occasionally recognized in small numbers in late lesions.

Spirochetes are demonstrable in about 70 per cent of the papules and maculopapules of syphilis.

There is no evidence that in either yaws or syphilis the spirochetes are phagocytosed by polymorphonuclear leukocytes or histiocytes.

There is no correlation between the titer of the Wassermann reaction of the blood and the presence or number of spirochetes in the cutaneous lesions of yaws.

Histologic criteria for the differentiation of the cutaneous and subcutaneous lesions of yaws and syphilis are in general unreliable.

SIMPLE ATROPHY OF THE LIVER

ITS RELATION TO INCREASED RESISTANCE

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DURHAM, N. C.

Simple atrophy of the liver, or brown atrophy, as it is more frequently called because of the presence of a brown pigment in the cytoplasm, has been recognized by pathologists since the time of Cohnheim.[1] Most authors of textbooks of pathology state that it occurs in senility and all forms of malnutrition. They also recognize that pressure either from tight clothing or from a tumor will cause it. These various ways of producing simple atrophy of the liver might be classed together as forms of malnutrition, local or general. Although extensive work has been done on the atrophy which occurs in passive congestion, a review of the literature reveals none on simple atrophy. Many writers have attributed the atrophy which is found with congestive heart failure to pressure around the central vein. Lambert and Allison [2] in a review of the various causes of atrophy and necrosis in passive congestion came to the conclusion that both are due to stasis. Therefore, it appears that fundamentally all forms of atrophy are the result of malnutrition.

Recently, MacNider [3] reported certain experiments which it is thought are of fundamental importance in regard to atrophy. In this work he called attention to certain morphologic changes which may develop in both renal and hepatic epithelium in the course of repair secondary to a severe injury of these tissues. Hepatic epithelium, following an injury of this order, as it regenerates is usually found arranged in cords which do not run toward the central vein as in the normal organ but are irregular in their configuration. The cells show, in general, a bizarre arrangement, with both branching and budding. The essential characteristic of this newly formed epithelial tissue is that it is flattened or occurs as a syncytial structure. The normal polyhedral cell has been replaced during the process of repair by an atypical flat-

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1. Cohnheim, J.: Lectures on General Pathology, English edition, London, The New Sydenham Society, 1889, sec. 2, p. 601.

2. Lambert, R. A., and Allison, B. R.: Bull. Johns Hopkins Hosp. **27**:350, 1916.

3. MacNider, W. de B.: J. M. Research **24**:425, 1911; J. Exper. Med. **49**:411, 1929; in Harvey Lectures, 1928-1929, Baltimore, Williams & Wilkins Company, 1930; Am. J. M. Sc. **178**:449, 1929; J. Pharmacol. & Exper. Therap. **56**:359 and 373, 1936.

tened cell. The sinusoids of the liver are greatly enlarged. There is no increase in connective tissue. Hepatic epithelium of this type is in a measure functionally effective, as is indicated by its ability to remove phenoltetrachlorphthalein from the plasma, and yet with such a degree of function it has been shown to have acquired distinct resistance to

Liver showing characteristic atrophy of hepatic cells and increased width of sinusoids; hematoxylin and eosin; × 100.

hepatoxic agents, such as uranium nitrate and chloroform. This observation by MacNider has recently been substantiated by Smyth and his associates [4] in their work on carbon tetrachloride poisoning. In addi-

4. Smyth, H. F.; Smyth, H. F., Jr., and Carpenter, C. P.: J. Indust. Hyg. & Toxicol. **18**:277, 1936.

tion to these observations MacNider [5] found that in twenty-one of the ninety-two dogs over 8 years old which were grouped as senile animals the liver had acquired, in association with the development of the senile state, a flattened, atypical epithelium in general similar to the epithelium which may develop in the liver of a dog in the process of repair following a severe injury. Those senile animals in which the hepatic epithelium was of the flattened, atypical form showed an acquired resistance to the action of chloroform, while control senile animals with hepatic cells of the normal type gave no evidence of resistance to this hepatoxic agent.

It is easily seen that the morphologic change described by MacNider is similar to, if not identical with, atrophy. Therefore, it appears that there is a relationship between simple atrophy and the body's resistance to toxic agents.

With these points in mind it was thought that a study of the occurrence of this change in a number of human livers would be of interest.

INVESTIGATIVE PROCEDURE

The material studied in the present investigation was made available through sections of livers obtained at 1,500 consecutive necropsies which have been performed in the department of pathology.

In order to prevent any particular age group from being overemphasized, the subjects were chosen so as to give a reasonable number in each of the following categories: those over 60, those in the fifth decade and those in the second decade. In order to ascertain whether there was any difference in the occurrence of such lesions in acute as contrasted with chronic disease, liver tissue from those persons whose deaths occurred as a result of lobar pneumonia and as a result of accidents was examined in one group, and that from persons with such chronic processes as tuberculosis and chronic nephritis, in another group. In making these studies all livers were excluded which were damaged to any extent by known processes; for example, chronic passive congestion, leukemia, tuberculosis, extensive postmortem changes, cirrhosis and metastases of malignant neoplasm.

OBSERVATIONS

Tissue from a total of 387 livers was studied. Such studies show many cytologic variations. Sections from the livers of eleven persons showed changes of a diffuse nature similar to those described usually as simple atrophy and in general identical with those described by MacNider as occurring in the liver of the dog in association with senility or developing in the process of repair following severe hepatic injury. The accompanying table gives the age of each person, the immediate cause of death and the number of hours elapsing between death and the time at which the necropsy was performed.

In these cases of atypical hepatic epithelium, the histories were carefully examined in order to see if there was any factor in the past life of the patient or in the present illness that might have produced the

5. MacNider, W. de B.: J. Pharmacol. & Exper. Therap. **56**:383, 1936.

aforementioned changes. Particular search was made for mention of the use of arsenic or of any other chemical which might have caused the hepatic damage which in turn provoked the abnormal type of hepatic repair. No correlation could be established between the changes in such tissue and any incidents in the histories of the patients. In some of the cases the damage to the liver may be attributed to a toxic factor and in others to senility, but in many these cannot be said to have played a part.

In the study of the livers, it was found that the commonest type of atrophy was associated with passive congestion. This change is similar in many respects to that described by MacNider except that it is generally more pronounced in the region of the central vein and less so at the periphery of the lobule. Also there is frequently necrosis around the central vein.

Data Pertinent to the Material

Immediate Cause of Death	Age	Hours Between Death and Necropsy
Poliomyelitis	45	5½
Sudden death from syphilitic heart disease	42	1
Death during abdominal operation	48	19
Osteomyelitis	43	2½
Septicemia	19	9
Pyonephrosis	52	3
Poliomyelitis	17	½
Automobile accident	26	20½
Meningioma	64	1
Diabetes	44	5
Hypertensive heart disease	46	6

It is of interest that none of the patients had any history of congestive heart failure. Also, they either did not show any anatomic evidence of congestion of the liver or showed a change so slight as to indicate that it was merely a terminal condition.

There is one other change in the liver which may be confused with the condition described. If the necropsy is deferred until after the autolytic processes have had time to advance one finds dilated sinuses and distorted liver cells.

COMMENT

In this paper are cited eleven instances of a diffuse change similar to that described by MacNider as an atypical type of repair. This change is identical with that which is usually called atrophy. The name given the change is unimportant. If, however, this morphologic change in man can be proved to have the same physiologic attributes as the changes MacNider and Smyth and his associates described as observed in dogs, this fact is highly significant.

Although every one is familiar with the increased resistance which a tissue may gain by having its usual type of cells replaced by nonfunc-

tioning cells, MacNider's experiments were the first to show that resistance of the fixed tissues could be augmented without loss of physiologic function and furthermore that this change in resistance was closely correlated with a change in morphologic appearance. This work, therefore, places on a firm morphologic basis the theory that has been intimated by others, namely, that the humoral and cellular concepts of Metchnikoff and Ehrlich are not sufficient to explain all the biologic phenomena of resistance and immunity. The recent work of Olitsky and his associates [6] and others, who showed that younger rats are more susceptible than older ones to nasal inoculation of a virus, adds support to this theory. Further experiments by these workers prove that this increased resistance was due neither to the presence of antibodies in the older rats nor to any general difference in the rats, as the old animals were not immune to intracerebral inoculation.

Although only eleven instances of this change were observed, it was noted that each liver had a morphologic character peculiar to itself. This same observation had previously been made by Soper and his associates.[7] The variation in many of the livers resembled the change in the ones cited. Those livers were excluded, however, because the change was not regarded as sufficiently diffuse or pronounced. That the liver from each patient should have an individual morphologic appearance is understandable since the liver is one of the chief detoxifying agents of the body and must, in the course of a lifetime, be subject to numerous and various traumas.

Although the conclusions drawn in this paper are based on an analogy between certain morphologic changes in the human liver and those in the dog, it is believed that further study will show that these changes in man are, as they are in the dog, associated with a changed physiologic response.

SUMMARY

Eleven instances of simple atrophy of the liver are described. It is pointed out that the changes noted are similar to those which have been described by MacNider and others as an atypical type of repair either following injury to the liver cells or resulting from senility. As MacNider has shown that dogs with livers of this type are more resistant to toxic substances, it is suggested that patients with hepatic cells of this type would also be more resistant to toxic agents. If this is true, it gives new importance to atrophy.

6. Olitsky, P. K.; Sabin, A. B., and Cox, H. R.: J. Exper. Med. **64**:723, 1936.

7. Soper, F. L.; Rickard, E. R., and Crawford, P. J.: Am. J. Hyg. **19**:549, 1934.

INTERALVEOLAR COMMUNICATIONS IN NORMAL AND IN PATHOLOGIC MAMMALIAN LUNGS

REVIEW OF THE LITERATURE

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Whether or not alveolar pores occur normally in mammalian lungs is an important consideration in determining the nature of the lining of the pulmonary alveoli. If interalveolar openings (pores, stomata, fenestrae) are present in the alveolar walls of the lungs of normal adult mammals, their presence tends to confirm strongly the view held by various authors that the pulmonary alveoli are not lined by a continuous epithelial membrane of endodermal origin.

In a study of the histologic structure of normal lungs from the common laboratory mammals by various methods, there were observed in thick stained sections (from 40 to 70 microns) numerous openings connecting adjacent alveoli. Since these openings were inconspicuous in ordinary thin sections of the expanded lungs, an experiment was devised to fill them with a stainable substance so that their relationship to the other constituents of the alveolar walls could be studied. This was accomplished by injecting intratracheally into the lungs of rabbits and rats heparinized blood plasma, previously prepared from other animals of the respective species. The plasma was allowed to clot, after which the lungs were removed, fixed in Zenker-acetic acid solution, embedded in pyroxylin, sectioned and stained by various methods.

The alveolar pores have also been studied in the lungs of dogs and monkeys rendered pneumonic and killed at different stages of the disease.

As a result of these observations it was concluded that the interalveolar openings are part of the normal structure of the alveolar walls and that they are one of the important avenues of intralobar spread of pneumococcic infection in experimental pneumococcic lobar pneumonia. This report includes the findings and experimental data on which these conclusions are based.

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The study of the normal lung material was carried out in the Department of Anatomy, in 1935.

This investigation was made possible by a grant to the Biological Science Division of the University of Chicago from the Rockefeller Foundation, a grant to the Department of Medicine from the Douglas Smith Foundation and by the aid of the Jessie Horton Koessler Fellowship fund of the Institute of Medicine of Chicago.

MATERIALS AND METHODS

Normal Animals.—Group 1. Three monkeys, three dogs, three cats, six rabbits, eight guinea pigs, five rats, six mice, and two opossums, all adults, were put to death for studies of normal lungs as follows: When an animal was to be killed, a lethal dose of pentobarbital sodium was injected intravenously into the larger animals and intraperitoneally into the smaller ones. The opossums were killed by insufflation of illuminating gas. When respiration had ceased, the chest and pericardial cavity were quickly opened, and the aorta clamped before the heart action had ceased. This procedure invariably produced congestion of the pulmonary vascular bed, which was desired to prevent collapse of the capillaries in the alveolar walls. A ligature was then applied firmly about the base of the heart to hold the blood in the vessels of the lungs when these were filled with the fixative and removed from the animals. Zenker-formaldehyde solution[1] was immediately injected intratracheally under low gravity pressure (from 8 to 15 cm. of water) until the lungs approximately filled the animal's thoracic cavity, care being taken not to overexpand the lungs. The trachea was ligated and the lungs and heart were removed in toto and placed in Zenker-formaldehyde solution for from five to eight hours.

Group 2. Two monkeys, two dogs, four rabbits, four guinea pigs, four rats and one opossum were put to death for studies with silver nitrate. The animals were killed with pentobarbital sodium as described for group 1, and 1.5 per cent silver nitrate solution was injected intratracheally into the lungs of half of each species group and into the opossum and intravenously into the lungs of the other half of the group, and these organs were fixed in solution of formaldehyde U. S. P. (1:10) for twenty-four hours. The details of this study will be given in another paper.

Group 3. Seven rats and four rabbits were used for the experiment in which plasma was injected. The heparinized plasma was previously prepared from blood obtained by puncture of the hearts of rats and rabbits other than those used in this experiment. One-half cubic centimeter of a solution of heparin (1 part of heparin to 500 parts of 0.85 per cent salt solution) was used to each 15 cc. of blood. The blood was cooled and centrifugated, after which the overlying plasma was removed by pipet, placed in tubes and kept in the refrigerator until ready for use. The animals were killed and the pulmonary vascular system was engorged in the manner described for group 2. The plasma, previously warmed to room temperature, was slowly injected intratracheally with a syringe until the lungs partially filled the thoracic cavity. A drop of plasma was placed on the pleural surface so that the time of clotting could be noted. When the plasma clotted, a small amount (depending on the size of the animal) of fixative was injected intratracheally, and the lungs and heart were removed in toto and placed for from five to eight hours in Zenker-acetic acid solution.

Pathologic Animals.—Fifteen monkeys and thirty dogs were infected intratracheally with doses of type I pneumococci that would permit survival, by the method devised by Robertson and his co-workers.[2] The animals were put to death at increasing intervals of time after they were infected, so that specimens of the lungs were obtained which showed all stages of the disease from the

1. This is Zenker's solution prepared with neutral solution of formaldehyde U. S. P. instead of acetic acid, in the proportions of 1 part of solution of formaldehyde to 9 parts of the Zenker stock solution.

2. Robertson, O. H., and others: J. Clin. Investigation **12**:393, 1933.

beginning (within one hour) to complete recovery. To obtain immediate fixation of the infected lungs, the animals were killed and the lungs prepared in the same manner as were the normal lungs in group 1.

The specimens both of normal and pathologic lungs were dehydrated, embedded in pyroxylin (nitrocellulose), sectioned (at from 8 to 70 microns), mounted serially on slides by the clove oil method [3a] and stained by the following technics: Normal lungs, group 1: hematoxylin-eosin-azure II for cytologic detail, Mallory's [3b] azan for connective tissue, orcein for elastic fibers and Foot's [3c] modification of Bielschowsky's stain for reticular fibers. Normal lungs, group 2: hematoxylin-eosin, hematoxylin-eosin-azure II, and Mallory's azan. Normal lungs, group 3: Weigert's fibrin stain, hematoxylin-eosin-azure II and Mallory's azan. Pathologic lungs: hematoxylin-eosin-azure II, Mallory's azan and Wallace's [3d] modification of the Gram-Weigert stain for fibrin and gram-positive bacteria.

OBSERVATIONS

Normal Lung: Thick Sections.—The interalveolar communications, designated as pores by most investigators of pathologic and histologic changes in the lungs, are most readily seen in thick sections of expanded lungs, in which the alveolar walls are viewed from their surfaces so that the light passes directly through them (fig. 9). These openings are located in the intercapillary spaces in the alveolar walls, and their relationship to the capillary network is seen best when the capillaries are filled with blood and the sections well stained. In such preparations varying numbers of openings are seen in the alveolar walls. They are most numerous in the lungs of dogs but occur frequently in the lungs of all animals studied. In every situation the alveolar walls contain from two to several openings. They appear to be more numerous in the septums subjacent to the pleura, where the alveoli are more expanded than in the deeper parts of the lung. In partially expanded lungs only the larger pores are seen.

The apparent size, shape and number of the pores depend on the degree of expansion of the lungs, the size of the intercapillary spaces and the pattern of the capillary network in the alveolar walls. They appear as round, oval, angular or slitlike openings, the diameters of which vary from a half of to two times the diameter of a red blood cell (fig. 9). Rarely are they seen to exceed the diameter of 2 red blood cells.

On viewing the alveolar walls in thick sections with an oil immersion lens and following the pores through the septums by focusing at different levels, many of them, especially the smaller ones, appear as channels or canals having a constant diameter throughout. Others are shaped like a funnel, having a larger opening on one side of the septum than on the other, while still others are constricted in the center of the

3. (*a*) Rubaschkin, W.: Anat. Anz. **31**:30, 1907-1908. (*b*) Heidenhain, M.: Ztschr. f. wissensch. Mikr. **32**:361, 1915. (*c*) Foot, N. C., and Menard, M. C. A.: Arch. Path. & Lab. Med. **4**:211, 1927. (*d*) Wallace, H. M.: Science **74**:369, 1931.

septum and thus have an hour-glass configuration. The larger pores, which are seen only in the walls of greatly expanded alveoli, have only the sharp margin of a thin membrane for their walls. The pores penetrate the alveolar walls at various angles to their surfaces. Some pass perpendicularly through the septums. Others pass at such an extreme angle that only by following them through the wall can the opening be seen on the other side of the septum. Some bend to conform to the shape of capillary walls which lie adjacent to them.

The walls of the pores are sharply outlined. They have smooth surfaces and are lined by the ground membrane which covers the capillary loop and encloses the reticular and elastic fibers (figs. 2, 9 and 10). Where the ground membrane closely invests the capillary, the wall of the pore appears to be formed only by the capillary wall. Other pores show a definite membrane between their margins and the capillary walls. This membrane may be wider on one side of the pore than on the other. A nucleus of an endothelial cell or a connective tissue cell may lie adjacent to the pore, forming a part of its wall (fig. 9). One or more reticular fibers may or may not encircle the pore, giving support to its walls (figs. 9 and 10). Elastic fibers, which are less numerous than reticular fibers in the alveolar walls, have not been observed to surround the pores completely. They appear to have no definite relation to the walls of the pores but are occasionally seen to encircle them partially as they pass in a more or less straight course over the alveolar walls.

Normal Lung: Thin Sections.—In thin (6 to 10 micron) sections of expanded lungs, the alveolar walls are usually cut tangentially, so that the pores are less easily seen. A detailed study of these sections, however, reveals partial or complete interruptions in the alveolar walls (figs. 2, 11 and 12). These are pores with diameters wider than the thickness of the sections, which have been cut so that parts of their walls appear in the serial sections preceding and following the section observed. The walls of some of the pores are completely intact, while the walls of others, which are incomplete, appear as cup-shaped depressions in the alveolar walls between the capillaries, the remaining portions of these walls appearing in either the preceding or the following serial section (figs. 1, 2, 3, 10, 11 and 12).

In thin sections of lungs from monkeys, cats, dogs, rabbits, guinea pigs and rats large free pigment-filled phagocytes, such as occur normally in adult mammalian lungs, are seen in some of the alveolar pores (figs. 6, 7, 10 and 11). The abundant cytoplasm of the phagocyte is usually constricted where it passes through the opening, to give the cell an hour-glass configuration (figs. 6, 7 and 10). Only a small strand of cytoplasm may extend through the pore, the greater bulk of the cell being located in one side of the septum. Phagocytes are seen which

occupy two pores at the same time, as if undecided which to use in passing from one alveolus to another. The nucleus of the phagocyte occupying the pore may be located on one side of the septum with most of the cytoplasm on the other side. The nuclei of some phagocytes are seen in the openings, where they also have an hour-glass shape. Binucleated phagocytes may have both nuclei on one side of the septum or one nucleus in the pore or a nucleus on each side of the septum.

Sometimes the alveolar phagocyte may fill the whole pore. At other times a distinct clear space can be seen between the cytoplasm of the phagocyte and the wall of the pore (figs. 2, 6, 7, 10 and 11). Some of the pores which contain phagocytes have had parts of their walls cut away when the lungs were sectioned, so that the cells are only partially surrounded as they lie across the septums (figs. 11 and 12). Such pores are sometimes seen to be twice as wide as the diameter of the protoplasm of the phagocytes which occupy them.

In sections of the lungs of one guinea pig a small localized area of inflammation was found. This area also showed polymorphonuclear leukocytes, which had migrated from the capillaries, in various stages of passing through the pores from one alveolus to another.

Some of the nucleated cells scattered over the alveolar walls lie in the pores and project freely into the adjacent spaces. They have the same relation to the openings as do the larger free alveolar phagocytes. The nucleated cells are approximately the same size and have finely granular vacuolated cytoplasm. In preparations made with hematoxylin-eosin-azure II the limits of these cells can be clearly seen. When the cells are in the pores they assume various shapes, but when they are located in the intercapillary spaces which are not perforated they are cuboidal. In either situation their cytoplasm does not cover the convexities of the capillaries.

Silvered Lungs.—In thick sections of silvered lungs interalveolar openings are also observed. They have, in these preparations, the same relationship to the other constituents of the alveolar walls as has been described. The mosaic pattern produced by the black lines in the walls of the alveoli mark the limit of the endothelial calls of the capillaries. The non-nucleated plates are not seen, and the nucleated cells in the intercapillary spaces of the alveoli are isolated and may be completely or only partially outlined by the silver nitrate.

Lungs into Which Plasma Was Injected.—Thin stained sections of the lungs of rabbits and guinea pigs into which heparinized plasma was injected intratracheally and allowed to clot before the lungs were fixed show large areas where the bronchi, alveolar ducts and alveoli are filled with plasma precipitate and a dense network of fibrin. The clotted fibrin in the alveoli forms a continuous intra-alveolar network,

which extends through the openings or pores in the alveolar walls (figs. 4, 5 and 9). From approximately every alveolus which contains the clotted fibrin, strands pass through from one to eight different openings in its walls into the neighboring alveoli. Strands of fibrin which cross the alveolar walls possess from 2 to 20 or more fibrin threads. The size, shape and number of the intra-alveolar openings which contain the fibrin are the same as those seen in the lungs not filled with plasma.

The walls of the fibrin-filled alveoli have the same appearance as the normal lungs not filled with plasma. The membrane covering the capillaries is smooth and also lines the openings through which the fibrin strands pass. An occasional free alveolar phagocyte is seen in the fibrin network, but there is no desquamation of the isolated nucleated cells from the alveolar walls. There is no cellular exudation or hemorrhage from the blood-filled capillaries. Nothing is observed in the fibrin-filled lungs to indicate that the interalveolar openings were formed by injury to the alveolar walls by the injection of the heparinized plasma.

Lungs with Experimental Pneumonia.[4]—In the earliest lesions (one or two hours after infection) the alveolar spaces are filled with edema fluid, serous precipitate, varying amounts of fibrin, pneumococci, varying amounts of blood leukocytes and red blood cells (figs. 20 and 21). The capillaries are greatly congested with white blood cells, and in many areas the leukocytes show all phases of migration from the capillaries into the alveolar spaces. The surfaces of the alveolar walls in the inflammatory area appear normal. The alveolar membrane over the capillaries is smooth, and the isolated nucleated cells are still present on the walls in normal numbers. Openings in the septums are frequently seen. Many contain fibrin, which extends across the septums and forms an intra-alveolar network such as is seen in the plasma-filled lungs of normal rats and rabbits (figs. 18, 19 and 20). Polymorphonuclear leukocytes can also be seen in the pores, with their processes extending for varying distances into the adjacent alveolar spaces. In areas where the alveolar spaces contain abundant edema fluid and numerous organisms, some of the pneumococci are also seen in the pores (figs. 15, 16, 17, 18 and 19).

The lungs from animals killed at four, eight, fifteen and twenty-four hours after being infected show increasing amounts of their respective inoculated lobes involved. At twenty-four hours, approximately the whole lobe is consolidated. The microscopic picture at the border of the spreading lesion as seen in the interval stages is the same (fig. 20). At the outer margin of the lesion the alveoli contain edema

4. The pathogenesis and pathologic changes of the experimental pneumonia will be given, with a discussion of the literature, in a separate paper.

fluid, pneumococci and a few polymorphonuclear leukocytes. The alveolar capillaries show little or no congestion with leukocytes. Just inside this area, toward the older portion of the lesion the alveoli contain many more leukocytes. The capillaries show congestion and active migration of leukocytes into the alveolar spaces. Polymorphonuclear leukocytes and strands of fibrin with pneumococci caught in them are frequently seen in the interalveolar openings (fig. 18). In the oldest portion of the lesion many cells (polymorphonuclear leukocytes, monocytes and phagocytes) are seen in various phases of passing from one alveolus to another, directly through the pore openings in the septums. Some of these polymorphonuclear leukocytes and mononuclear macrophages contain ingested pneumococci. In all the stages of the development of the pneumococcic infection, organisms are rarely seen in the substance of the alveolar walls or in the lumens of the blood capillaries or of the larger lymphatics.[5] The great majority of the pneumococci are in the alveolar spaces, with some adhering to the surfaces of the alveolar walls.

For twenty-four hours after the onset of the infection the alveolar walls show no significant local changes. After this time the nucleated cells on the alveolar walls begin to hypertrophy, proliferate and desquamate. This reaction continues throughout the remaining course of the disease. At from forty-eight to seventy-two hours the septums are slightly thickened and possess many more nucleated cells than are seen in normal lungs (fig. 21). In these preparations, also, the alveolar pores are frequently seen. They have the same size, shape and relation to the other constituents of the walls as in normal lungs. Some of the pores are noted as empty open spaces; others are filled with strands of fibrin. The alveolar phagocytes which are present in large numbers in the alveolar spaces are frequently seen in the openings in the alveolar walls (figs. 13, 14 and 21).

In the lungs of animals which have completely recovered from the pneumococcic infection, the septums have the same appearance as those in the noninfected lungs. Nucleated cells are present in the alveolar walls, in normal numbers. Interalveolar openings are frequently seen in the septums and in every way resemble those seen in the noninfected lungs.

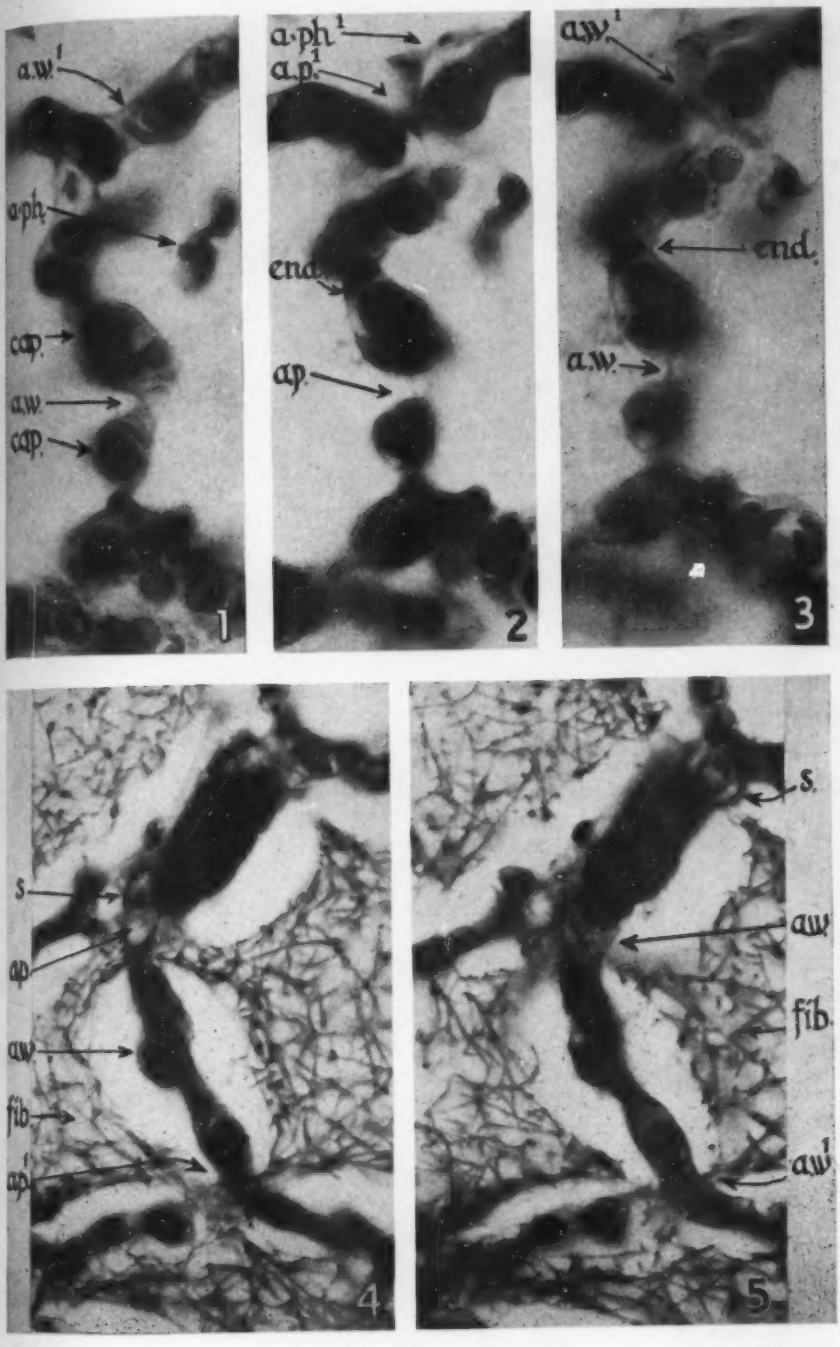
5. One dog was infected with 10 cc. of an eighteen hour broth culture of Pneumococcus type I, which was concentrated in 4 cc. of gelatin-Locke solution. The animal was killed after one and a half hours. The sections of the lungs showed only one area of beginning cellular reaction and edema of the walls of vessels. Pneumococci were more frequently found in the interstitial tissue of the walls of the bronchi and blood vessels and in the lymphatic spaces, and occasional ones were seen in the lumens of the blood capillaries. The great majority of pneumococci, however, were observed in the alveolar spaces, free and adhering to the alveolar walls.

EXPLANATION OF FIGURES 1 TO 5

Figures 1, 2 and 3 are photomicrographs of a normal alveolar wall of a dog's lung taken at three different planes of focus. Figure 1 shows the upper plane. Here the alveolar wall at points *a.w.* and *a.w.*[1] is seen intact. Figure 2, showing the middle plane, discloses two complete interruptions in the alveolar walls at *a.p.* and *a.p.*[1]. These are alveolar pores, one of which (*a.p.*[1]) contains a free pigment-filled alveolar phagocyte (*a-ph.*[1]). The upper portion of the walls of these openings is in the upper plane of focus and designated in figure 1 as *a.w.* and *a.w.*[1], respectively. Figure 3, representing the lower plane of focus, shows the lower portion of the walls (*a.w.* and *a.w.*[1]) of the alveolar pores which are seen in figure 2. Ten micron section; hematoxylin-eosin stain; magnification, × 1,000.

Figures 4 and 5 are photomicrographs taken at two planes of focus of a 10 micron section of normal rat's lung filled with heparinized plasma, which was allowed to clot. Figure 4 shows the upper plane, in which the alveolar spaces are filled with a network of strands of fibrin, which pass through openings (*a.p.*, *a.p.*[1]) in the alveolar walls. These are alveolar pores, the upper walls of which appear in the preceding serial section. Figure 5, showing the lower plane, presents the lower portion of the walls (*a.w.*, *a.w.*[1]) of these pores intact. Microscopically the alveolar walls appear normal. Mallory's azan technic; magnification, × 1,000.

Key to labels *a.p.*, alveolar pore; *a.ph.*, alveolar phagocytes; *a.w.*, alveolar wall; *cap.*, capillary filled with red blood cells; *end.*, endothelial cell of capillary wall; *fib.*, fibrin network; *s.*, septal cell.



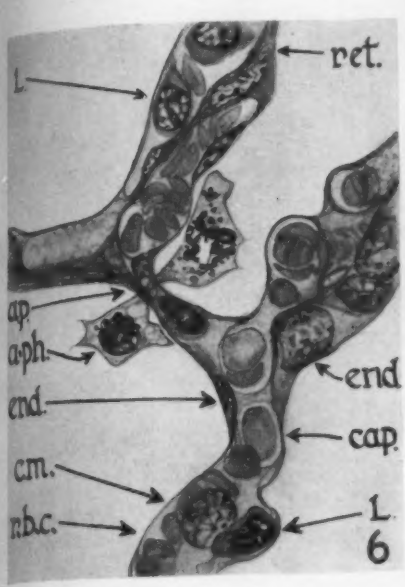
Figures 1 to 5.

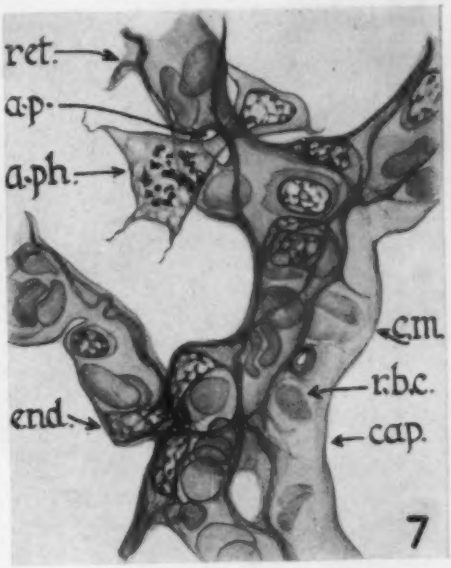
EXPLANATION OF FIGURES 6 TO 8

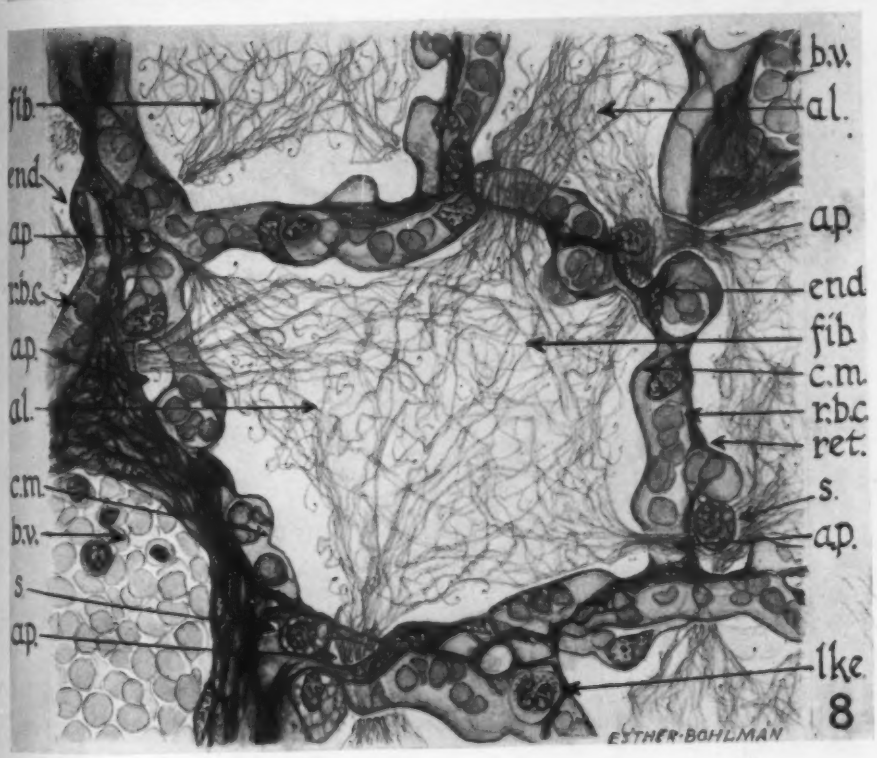
Figures 6 and 7 are camera lucida drawings of alveolar walls of the lungs of normal monkeys (10 micron sections) showing pigment-filled macrophages in the alveolar pores (*a.p.*). Mallory's azan technic; Leitz 2 mm. apochromatic objective and × 15 ocular; camera lucida at stage level.

Figure 8 is a camera lucida drawing of a normal rat's lung (10 micron section) filled with heparinized plasma, which was allowed to clot. The alveoli are filled with a fibrin (*fib.*) network and are connected by strands of fibrin through openings (*a.p.*) in the alveolar walls. Microscopically the alveolar septums appear normal. Mallory's azan technic; Bausch and Lomb 2 mm. objective and × 10 ocular.

Key to labels: *al.*, alveolar space; *a.p.*, alveolar pore; *a.ph.*, alveolar phagocyte; *b.v.*, blood vessel; *cap.*, blood capillary; *c.m.*, capillary membrane; *end.*, endothelial cell of capillary; *fib.*, fibrin network; *L.*, lymphocyte; *lke.*, granular leukocyte; *r.b.c.*, red blood cell; *ret.*, reticulum; *s.*, septal cell.







Figures 6 to 8.

EXPLANATION OF FIGURES 9 TO 14

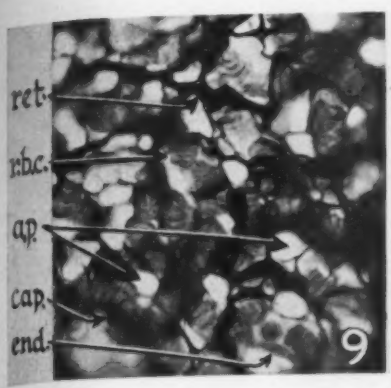
Figure 9 is a photomicrograph of a thick (60 micron) section of a normal lung from a dog, showing the surface of an alveolar wall. The capillaries are filled with red blood cells. Some of the spaces between capillaries are perforated (*a.p.*).

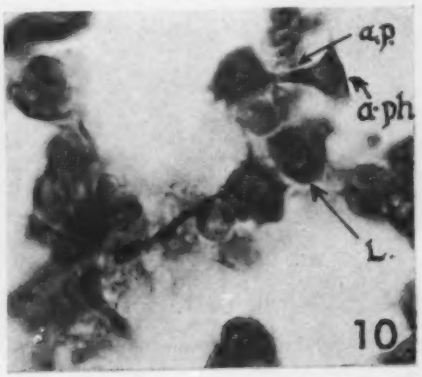
Figure 10 is a photomicrograph of a thin (10 micron) section of a normal lung from a monkey, showing a pigment-filled alveolar phagocyte in an alveolar pore (*a.p.*). Figure 7 is a camera lucida drawing of this area. The lumen of the pore appears as a clear area surrounding the constricted portion of the cell (*a.ph.*). This pore has approximately the same diameter as those seen in the dog's lung (fig. 9).

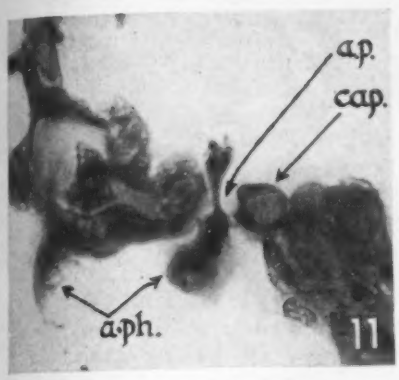
Figures 11 and 12 are photomicrographs taken at two planes of focus of a thin (10 micron) section of a normal lung from a monkey, showing a free alveolar phagocyte in a pore. The upper portion of the wall has been cut away and appears in the preceding serial section. Figure 11 is at the level of the pore opening, which is indicated by the clear spaces on each side of the alveolar phagocyte (*a.ph.*). Figure 12 is at the lower level and shows the lower wall of the pore. Figures 9, 10, 11 and 12 are stained with Mallory's azan technic. Figure 9 is also stained with Foot's reticulum stain.

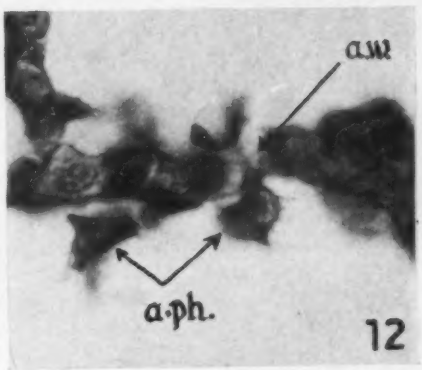
Figures 13 and 14 are photomicrographs of a pneumonic lung of a dog killed at the time of recovery, seventy-six hours after infection. The section shows many alveolar phagocytes and polymorphonuclear leukocytes in the alveolar spaces and in the pores. Figure 13 is the upper level of a section showing an alveolar phagocyte in a pore (*a.p.*). The upper portion of the pore wall has been cut away and appears in the preceding serial section. The portion of the alveolar wall marked (*a.w.*) is the upper portion of the wall of the pore which appears in the lower plane of focus in figure 14. Figure 14 shows the lower portions of the wall of the pore which appears in figure 13. The pore appearing in figure 14 also contains an alveolar phagocyte (*a.ph.*[1]). Hematoxylin-eosin-azure II; magnification, × 1,000.

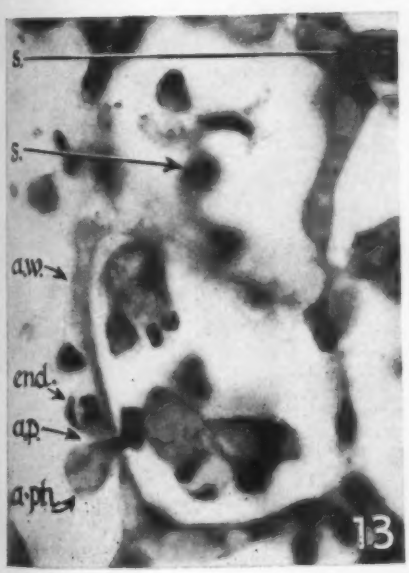
Key to labels: *r.b.c.*, red blood cell; *a.p.*, alveolar pores; *a.ph.*, alveolar phagocyte; *a.w.*, alveolar wall; *cap.*, blood capillary; *end.*, capillary endothelial cell; *L.*, lymphocyte; *mo.*, monocyte; *ret.*, reticulum; *s.*, septal cell.

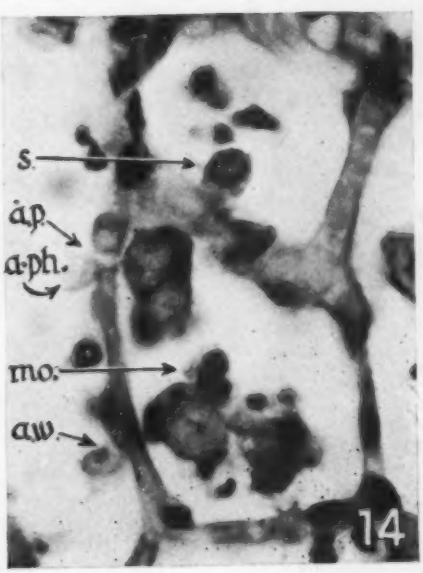












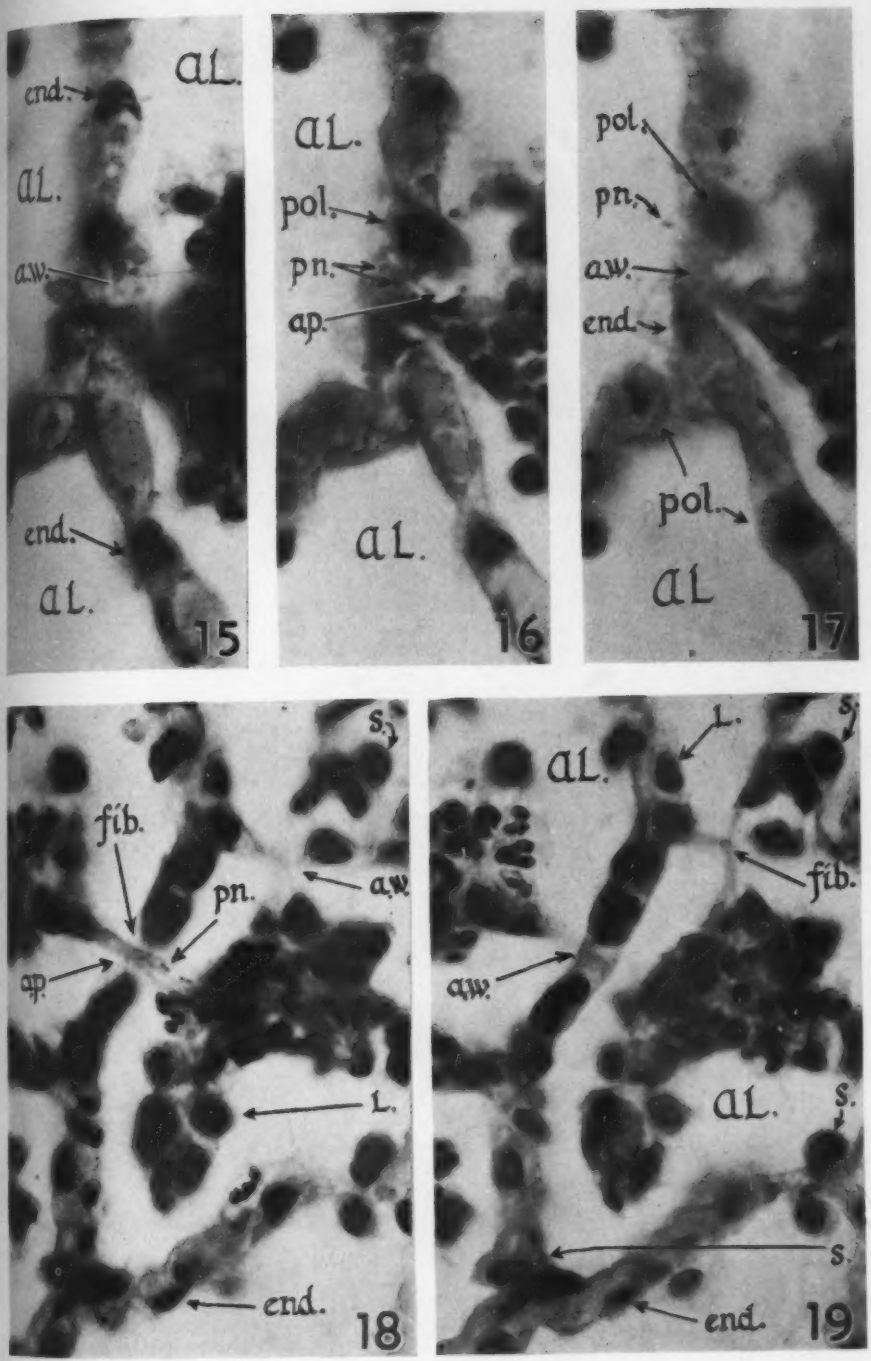
Figures 9 to 14.

EXPLANATION OF FIGURES 15 TO 19

Figures 15, 16 and 17 are photomicrographs taken at three planes of focus of a thinly (10 microns) sectioned lung of a monkey killed four and a half hours after infection with type I pneumococci. Figure 15 is the upper plane of focus showing the upper portion of the wall (*a.w.*) of the pore which appears in the middle plane of focus shown in figure 16 (*a.p.*). Figure 16, taken through the plane of the lumen of the aforementioned pore, shows it filled with polymorphonuclear leukocytes and pneumococci. Figure 17 is the lower plane of focus, showing the lower portion of the wall (*a.w.*) of the pore (*a.p.*) which appears in figure 16. Hematoxylin-eosin-azure II; magnification, × 1,000.

Figures 18 and 19 are photomicrographs taken at two planes of focus, of a thinly sectioned (10 microns) lung of a monkey killed fourteen and a half hours after infection with type I pneumococci. Figure 18 is the upper level, which shows a fibrin strand containing two pneumococci extending from one alveolus to another through an alveolar pore (*a.p.*). The upper portion of the wall of the pore appears in the preceding serial section. The point of the alveolar wall marked *a.w.* in figure 18 is the upper portion of the wall of the pore through which fibrin (*fib.*) passes in the lower plane of focus (fig. 19). In figure 19 is also shown the lower portion of the wall (*a.w.*) of the pore which appears in figure 18. The capillaries are filled with leukocytes. The alveolar walls show no desquamation of septal cells at this stage. Hematoxylin-eosin-azure II; magnification, × 1,000.

Key to labels: *al.*, alveolus; *a.p.*, alveolar pore; *a.w.*, alveolar wall; *end.*, capillary endothelial cell; *fib.*, fibrin; *L.*, lymphocyte; *pol.*, polymorphonuclear leukocyte; *pn.*, pneumococcus; *s.*, septal cells.



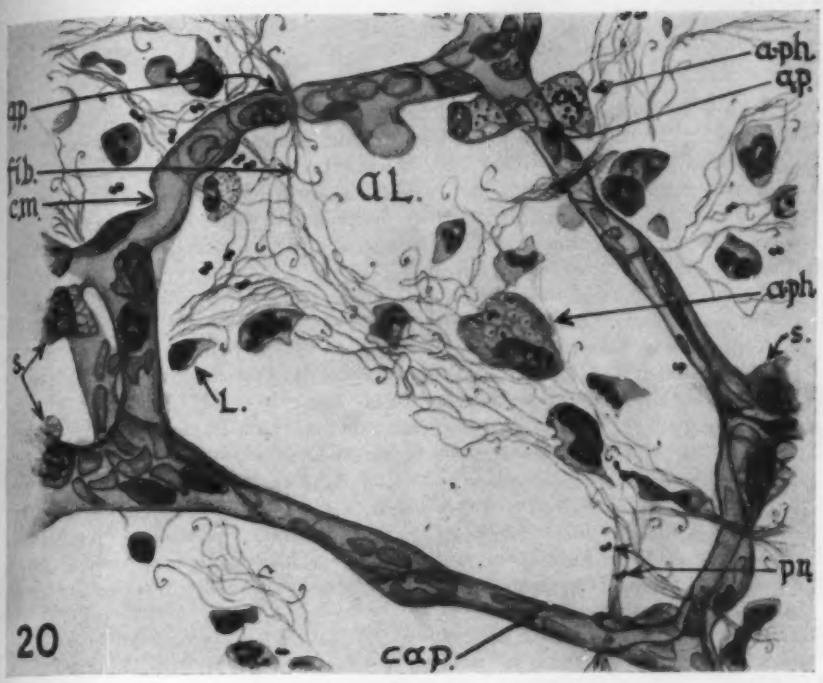
Figures 15 to 19.

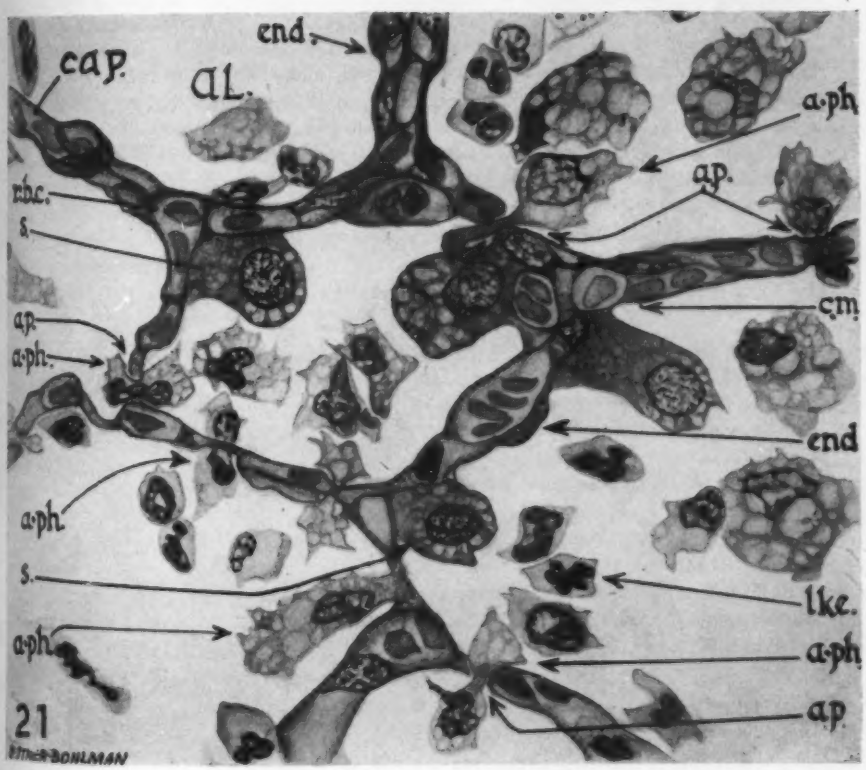
EXPLANATION OF FIGURES 20 AND 21

Figure 20 is a camera lucida drawing (made at two levels) of a thinly sectioned (10 microns) lung of a dog infected intratracheally with type I pneumococci and killed after two and a half hours. The drawing represents the margin of a lesion in which the alveoli contained fibrin (*fib.*) connected through pores (*a.p.*) in the alveolar walls and a few inflammatory exudate cells. At this stage there is no desquamation of cells from the walls, which have a normal appearance. Hematoxylin-eosin-azure II; Bausch and Lomb 2 mm. objective and × 10 ocular; camera lucida at stage level.

Figure 21 is a camera lucida drawing of a thinly sectioned (10 microns) lung of a dog which was infected intratracheally with type I pneumococci and killed after seventy-six hours (just after recovery). At this stage of the disease the alveoli are filled with a few polymorphonuclear leukocytes (*lke.*), lymphocytes (*L.*), and many large mononuclear phagocytes (*a.ph.*). The alveolar walls show marked proliferation of cells (*s.*). The portion of the alveolar walls between the cells has a normal appearance. The alveolar walls also contain many openings (pores, *a.p.*) which are made conspicuous by the presence of macrophages (*a.ph.*) in them. Hematoxylin-eosin-azure II; Bausch and Lomb 2 mm. objective and × 10 ocular; camera lucida at stage level.

Key to labels: *a.p.*, alveolar pore; *a.ph.*, alveolar phagocyte; *cap.*, blood capillary; *c.m.*, capillary membrane; *end.*, capillary endothelial cell; *fib.*, fibrin; *L.*, lymphocyte; *lke.*, polymorphonuclear leukocyte; *pn.*, pneumococcus; *r.b.c.*, red blood cell; *s.*, septal cell.





Figures 20 and 21.

LITERATURE

It will be impossible to give all the discussions which various authors have published on this interesting subject, for the question of the communication between neighboring alveoli has been discussed vigorously and for a long time. Because some of the investigators at first concluded that the pores do not occur normally in the lungs and after further investigations became convinced that the pores are normal constituents of the alveolar wall, the literature has more meaning when reviewed in chronological order.

Adequate reviews of the early studies can be found in the papers of Williams [6] (1859) and Miller [7] (1902 and 1937). Of the early literature, it will be necessary to mention only Reisseissen [8] (1822), Rossignol [9] (1847) and Schultze [10] (1871), who maintained that the terminal portions of the bronchial tree end as blind sacs or vesicles, while, on the other hand, Rainey [11] (1855), Kölliker [12] (1854 and 1867), Zenker [13] (1862), von Luschka [14] (1863) and Henle [15] (1873) thought that they saw small communications between the terminal vesicles. Henle [15] considered the openings as being abnormally formed by atrophy and resorption of the alveolar walls and suggested that they might be the origin of pulmonary emphysema. Although Kölliker [12] described openings in the terminal portions of the bronchi of man, he made no mention of them in his very important monograph (1881) [16] on the structure of the lungs of man as observed following intratracheal injection of a solution of silver nitrate.

Delafield [17] (1882), after a study of normal and pathologic lungs of man, asserted that openings in the alveolar walls occurred normally. Roosevelt [18] (1890) maintained that when perfect casts were made of an ultimate bronchus

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and its air vesicles the latter looked like a bunch of spheroid berries and were attached to one another at two or more points. The views of Roosevelt and Delafield were opposed by Miller [19] (1892 and 1893), who found no communications between the air cells of the air sacs or between the walls of one lobule and those of another in his reconstruction and corrosion preparations of lungs of the dog, cat, rat, rabbit and sheep. Miller also carried out experiments in which he injected fluid into a secondary bronchus and found that the injected substance remained confined to the branches of the bronchus and did not fill the remaining lung. He also injected pyroxylin (celloidin) of different colors into secondary bronchi and found that it did not spread beyond the branches of these bronchi.

New interest was aroused in the interalveolar communications in mammalian lungs by Kohn's [20] (1893) microscopic description of lungs affected by acute fibrinous pneumonia and of lungs undergoing carnification. In the pneumonic lungs he saw strands of fibrin extending from one alveolus to another through openings in the alveolar walls. In the lungs undergoing carnification he saw strands of tissue extending across the walls through similar openings. He raised the question whether these openings were normal or pathologic entities but leaned toward the latter view. Hauser [21a] (1893), under whom Kohn studied, considered such openings normal and again (1894) described them in lungs affected by acute fibrinous pneumonia and referred to them as the "pores of Kohn." [21b] Ribbert [22] (1894) and his students Bezzola [23] (1894) and Herbig [24] (1894), from their studies of pneumonic lungs, held that the "pores of Kohn" are pathologic products of the inflammation which causes the desquamation of the respiratory epithelium with subsequent formation of the openings. Virchow [25] (1895) maintained that the pores are formed by pathologic processes, although it was hard for him to believe that they are not normal constituents of the alveolar walls.

In 1895 Hansemann [26] reported an experiment in which he injected intratracheally into the lungs of rats, guinea pigs and rabbits water-soluble berlin blue mixed with gelatin, fixed the lungs in alcohol, sectioned them and stained the sections with Van Gieson's mixture. He observed strands of gelatin passing through from two to six openings in each alveolar wall, into the neighboring alveoli. He concluded that these openings were the same as those Kohn described in the pneumonic lungs of man and held that they were normal constituents of the alveolar walls. Ebner [27] (1898) and his student Aigner [28] (1899) repeated Hansemann's experiments on rats and rabbits and held that the strands of gelatin

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25. Virchow, R., in discussion on Frankel, A.: Berl. klin. Wchnschr. **32**:129, 1895.

26. Hansemann, D.: Sitzungsb. d. k. preuss. Akad. d. Wissensch. **2**:999, 1895.

27. von Ebner, V., in von Kölliker, A.: Handbuch der Gewebelehre des Menschen, ed. 6, Leipzig, W. Engelmann, 1898, vol. 3, p. 297.

28. Aigner, A.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Kl. **108**: 11, 1899.

that Hansemann described as passing through the pores only stuck to the alveolar surfaces or passed over the openings of the alveoli adjoining the alveolar ducts. They could not see communications between the adjacent alveoli and concluded that interalveolar openings form only as a result of inflammation and emphysema and that Hansemann's pores were fixation artefacts.

While studying the problem of emphysema in Hansemann's laboratory, Sudsuki [29] (1899) repeated Hansemann's experiments and confirmed his findings. Both Hansemann and Sudsuki held that the alveolar pores are unimportant in the production of pulmonary emphysema. In 1900 Hansemann [30] again upheld his original findings and asserted that Aigner's negative results were due to injecting a gelatin mass which was too thick and viscid to pass through the pores. At this time Hansemann also reported openings in silver nitrate preparations of the lungs of man, orang-utan, chimpanzee, baboon, dog and mouse. He emphasized the importance of thick, well stained preparations in demonstrating the pores and pointed out that the elastic fibers have no fixed relation to them.

Piersol [31] (1895) held that the pulmonary alveoli communicate only with their infundibuli. Laguesse and d'Hardiviller [32] (1898) in several years' study of growing lungs seldom saw communications and asserted that age played a part in their formation and that therefore the communications were not normal structures. Miller [7] reaffirmed his original convictions without adding new evidence that the alveolar pores do not occur in normal lungs. Laguesse [33] (1901), from his study of casts, reconstruction preparations and stained sections of lungs, concluded that the alveolar pores are only temporary structures and cannot be clearly demonstrated in healthy adult lungs. Merkel [34] (1902) could not find the pores in the new-born but verified their existence in lungs of the young cat and in adult man.

Other investigators, Renaut [35] (1897), Nicolas [36] (1898), Zimmermann [37] (1900), Linser [38] (1900) and Sobotta [39] (1902) maintained that interalveolar communications occur normally in mammalian lungs. Nicolas and Linser described and demonstrated elastic fibers encircling the pores, giving support to their walls. Oppel [40] (1905) could not find alveolar pores in the lower mammals that he had studied, and only rarely did he see them in the lungs of man. He considered

29. Sudsuki, K.: Virchows Arch. f. path. Anat. **157**:438, 1899.

30. Hansemann, D.: Arch. f. mikr. Anat. **55**:337, 1900.

31. Piersol, G.: Textbook of Normal Histologie, ed. 4, Philadelphia, J. B. Lippincott Company, 1897, p. 252.

32. Laguesse, E., and d'Hardiviller, A.: Bibliog. anat. **6**:125, 1898.

33. Laguesse, E.: Trois leçons sur la structure du poumon, Paris, Vigot frères, 1904.

34. Merkel, F.: Atmungsorgane, in von Bardeleben, K.: Handbuch der Anatomie des Menschen, Jena, Gustav Fischer, 1902, vol. 6, p. 182.

35. Renaut, J.: Traité d'histologie practique, Paris, Lecrosnier & Babé, 1897, vol. 2, p. 489.

36. Nicolas, A.: Appareil respiratoire, in Poirier, Paul: Traité d'anatomie humaine, Paris, L. Battaille & Cie, 1898, vol. 4, p. 524.

37. Zimmermann, K. W.: Anat. Anz. **18**:373, 1900.

38. Linser, P.: Anat. Hefte **13**:307, 1900.

39. Sobotta, J.: Atlas und Grundriss der Histologie und mikroskopischen Anatomie des Menschen, Munich, J. F. Lehmanns, 1902.

40. Oppel, A.: Atmungsapparat, in Lehrbuch der vergleichenden mikroskopischen Anatomie der Wirbeltiere, Jena, Gustav Fischer, 1905, vol. 6, p. 723.

the pores, as did Henle,[15] to be pathologic products of atrophy and resorption of the alveolar walls, with age playing a prominent part in their formation.

New impetus was given to the study of the alveolar pores when Schulze [41] (1906), who denied their existence in normal lungs in 1871, published his studies on the comparative anatomy of the lung. Employing thick sections of lungs previously filled with silver nitrate and of others stained by various methods, he observed smooth-edged round or oval openings in all the lungs of the adult mammals, young and old, that he studied. These openings were most numerous in the lungs of Insectivora (the mole and especially the hedgehog). They were less abundant in the lungs of Chiroptera and Rodentia. The pores were rarely seen in the lungs of Edentates, and when noted they were single and small. Schulze also observed the pores frequently in the lungs of several domestic animals but less so in man. As a result of this study Schulze concluded that the pores are normal constituents of the alveolar walls of mammalian lungs.

In 1906 Mueller [42] published the results of an extensive comparative histologic study of the lungs of the common domestic animals, including the horse, ox, sheep, goat, pig, dog, cat and rabbit. He fixed the lungs in absolute alcohol and 4 per cent formaldehyde by intratracheal, intravascular or intrapleural injections, embedded them in paraffin, sectioned them at from 9 to 30 microns and stained the sections with hematoxylin, eosin and Weigert's elastic tissue stain. Another series of lungs were stained by silver nitrate after Kölliker. He again stressed the importance, as did Hansemann and Schulze, of having thick, well stained sections of expanded lungs in order to see the pores. Under these conditions he concluded that the gelatin injection method of Hansemann offered no advantage for demonstrating the pores in the alveolar walls. Mueller, however, was not sure the openings he saw were of the same type as those which Hansemann described, for the latter considered the pores as canals, and Mueller saw them as holes with sharp margins in the thinnest part of the membrane. Mueller considered this difference in observation to be due to variation in the degree of expansion of the alveolar walls and whether the capillaries were well filled. He noted that when the capillaries were filled with blood or some injection mass, thus increasing the thickness of the alveolar walls, the pores did appear as canals in many places. However, Mueller wondered if one could consider them normal formations, because he could not find these openings in the lungs of young animals (cat, dog, calf, colt).

Miller [43] (1907), in a short paper criticizing Schulze's and Mueller's interpretation of the structure of the pulmonary lobule, continued to deny the presence of interalveolar communications in mammalian lungs. Laguesse, on the other hand, who denied the existence of alveolar pores in 1901, after several years' study of the lung was so impressed by Schulze's observations and illustrations that he set himself and his student, Marchand, to the task of solving the problem of the alveolar pores in man and other mammals. Laguesse and Marchand [44] (1911) and Laguesse [45] (1912) reported their findings in the lungs of a 26 year old man. These lungs had been freshly fixed intratracheally with 70 per cent alcohol, sectioned at from 5 to 50 microns and stained by the safranin trinitrophenol-noir naphthol method of Curtis and with Weigert's elastic tissue stain.

41. Schulze, F. E.: Sitzungsb. preuss. Akad. wissensch. phys.-math. Kl. **6**: 225, 1906.

42. Mueller, J.: Arch. f. mikr. Anat. **69**:1, 1906.

43. Miller, W. S.: Anat. Rec. **1**:61, 1907.

44. Laguesse, E., and Marchand, R.: Compt. rend. Soc. de biol. **70**:178, 1911.

45. Laguesse, E.: Compt. rend. de l'Assoc. d. anat. **14**:142, 1912.

Studying these sections under high power magnification and an oil immersion lens, with a white or yellow light, he observed a varying number of triangular, round and oval openings with clearcut borders in the alveolar walls. Each alveolar wall contained from one to seven openings, which occurred in the intercapillary spaces not occupied by the epithelial cells. The holes varied in diameter from 2 to 13 microns and rarely were elastic fibers seen encircling them. In thin (5 micron) sections he observed that these openings appeared as partial and as complete interruptions in the alveolar walls.

Marchand [46] studied the lungs of the young adult hedgehog, mole, rat, bat, pig, sheep and man with the methods employed by Laguesse. Marchand observed openings from 2 to 10 microns in diameter in the intercapillary spaces of the alveoli in all the animals studied. They varied in number in the various animals, being most numerous in the lungs of the hedgehog, bat, mole and rat, but regularly occurred in the lungs of the sheep, pig and man. Marchand also studied the lungs of mature fetuses of the hedgehog, rat and man but could find no pores. In his postnatal series of lungs of the rat, cat and man, he found pores first in a rat, forty hours after birth, in which one in three alveolar surfaces showed one or two pores. The number increased somewhat in the lungs of a 3 week old rat. He could find no pores in the lungs of a 3 week old cat, but they were present in a 5 month old animal. Pores were not seen in the lungs of human infants up to 10 months of age. He concluded that pores probably appear in the lungs of infants at the end of the first year or at the beginning of the second, and thereafter are present constantly in small numbers. The observations of Laguesse and Marchand confirmed those of Schulze, and they readily accepted pores as normal structures in the alveolar walls of mammalian lungs and considered that these pores, although small in man, were capable of acquiring much importance from the physiologic point of view in certain animal species.

Caradonna [47] (1913) saw pores in the lungs of the guinea pig, horse, rabbit and dog and at first considered them normal communications. He later became interested in the question raised by Mueller [42] as to whether the pores could be considered normal in view of the fact that they do not occur in the lungs of young animals. He examined the lungs of young guinea pigs and rabbits and found that the pores appeared only at about 8 months of age. He then devised an experiment to determine the cause of their formation. Obtaining two groups of guinea pigs, he kept one group isolated from the other and in a state of rest, tranquillity and repose, and he found that the pores did not appear in the lungs of this group until the fourteenth or fifteenth month, and then only rarely. The animals of the second group were kept together in a narrow pen, and three times a day, usually at meal time, they were molested for at least ten minutes to put them in a state of extreme excitement, so that rapid breathing resulted. In these animals perforations were first seen in the alveolar walls about the third and fourth months and became more numerous thereafter until, after a year, the condition became emphysema-like. Caradonna concluded that the so-called normal communications between the alveoli are only the product of excessive effort and dilatation of the alveolar walls during the act of respiration.

In his paper on the structure of the lobule of the lungs of the cat as shown in reconstruction preparations made from thick (20 micron) sections of the lung Miller [48] (1913) reported no interalveolar communications and firmly maintained

46. Marchand, R.: (*a*) Compt. rend. Soc. de biol. **70**:912, 1911; (*b*) Bibliog. anat. **22**:57, 1912.

47. Caradonna, G.: Arch. ital. de biol. **60**:92, 1913.

48. Miller, W. S.: J. Morphol. **24**:459, 1913.

anew that the pores are not normal structures. He asserted that they can be caused by anything which produces a separation of the epithelial cells or rupture of the delicate framework of the septums, such as overdistention, inflammation, desquamation of epithelium, atrophy and age.

Carrying on his controversy with Miller on the structure of the pulmonary lobule and the problem of the alveolar pores, Schulze [49] (1915) reaffirmed his view that the pores are normal constituents of the alveolar walls, occurring between the epithelial plates in the intercapillary spaces. He presented a good stereophotogram of a thick section of the lung of a bat, showing numerous openings in the intercapillary spaces of the alveolar septums.

While working under Schulze, Oertel [50] (1919) studied the lungs of various animals of different ages for a number of years. For his studies of lungs he considered the gelatin injection method of Hansemann and wax reconstruction methods too crude, and specimens of pneumonic lungs were not at his disposal. So he applied various staining methods to sections from 3 to 60 microns in thickness. He observed the pores in all the animals studied, and being aroused by the failure of Miller to demonstrate pores in reconstruction preparations of the lungs of various animals in which he himself had seen them, he made a wax reconstruction of a lung of a bat. The lungs had been expanded with silver nitrate solution, embedded in paraffin, serially sectioned 5 microns in thickness and mounted without further staining. In thin sections he saw complete interruptions in the alveolar walls, which were the pores cut tangentially. He then carefully traced the thin lung sections on wax plates and produced in the reconstruction the openings in the alveolar walls. They had a regular distribution and connected the alveoli of the same bronchus as well as those of one bronchus with those of another. They were round or oval with sharp borders and with diameters equal to that of an erythrocyte, but they varied somewhat in size depending on the degree of expansion of the lung. From his study of the lungs of the bat, man and other mammals, Oertel maintained that the reason Miller did not see openings in his reconstruction was because Miller used sections of lung which were so thick (20 microns) that the pores did not appear as complete interruptions, a condition necessary for them to be represented in the reconstructed alveoli.

Ogawa [51] (1920), while making a histologic study of the respiratory spaces of the lungs of vertebrates, observed pores in the lungs of the mole, bat, rat, guinea pig, rabbit, cat and dog and pointed out, as did earlier authors, that to see pores it is necessary only to have thick sections in which the alveolar walls are darkly stained. He noted that, although the pores were present normally, their number and size varied in the same animals. Ogawa could distinguish the pores from artificial breaches in the septums because the former had smooth borders and were round or elliptical, and he observed that the elastic and reticular fibers may or may not encircle them.

Other workers, Loeschcke [52] (1921), Heiss [53] (1922) and Beitzke [54] (1928), are all of the opinion that the pores are normal structures in the lungs of mam-

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49. Schulze, F. E.: Sitzungsb. preuss. Akad. Wissensch. Phys.-math. Kl. **14**: 258, 1915.

50. Oertel: Sitzungsb. Heidelberg. Akad. Wissensch. Math.-naturw. Kl., 1919, vol. 10, no. B 12.

51. Ogawa, C.: Am. J. Anat. **27**:333, 1920.

52. Loeschke, H.: Beitr. z. path. Anat. u. z. allg. Path. **68**:213, 1921.

53. Heiss, R.: Ergebn. d. Anat. u. Entwcklngsgesch. **24**:244, 1923.

54. Beitzke, H.: Atmungsorgane, in Aschoff, K.: Pathologische Anatomie, Jena, Gustav Fischer, 1928, chap. 7, p. 283.

mals, although they are less numerous in the lungs of man. Although Loeschcke studied normal and pathologic lungs of man by injection methods, using pyroxylin (celloidin) and metal, the casts showing large connections between the alveoli, he stated that the best way to see these openings in their natural form is to examine stereoscopically thick sections of lungs fixed in solution of formaldehyde.

Miller [55] (1923 and 1925), who for thirty-five years has maintained the opinion that the alveolar pores are artefacts and that the alveoli are lined by a continuous layer of uninterrupted epithelium, described the formation of pores in fibrinous pneumonic lungs and in lungs from persons who had mitral stenosis. He held that the initial factor in the formation of the pores is the accumulation of serum behind the epithelial cells, which causes them to desquamate. The accumulation of serum, produced either by inflammation or by mechanical congestion, must cause the epithelium to be shed from diametrically opposite sides of an alveolar wall before a pore can be formed. The shedding of the epithelium on only one side of an alveolar wall does not result in pore formation. Thus he maintained that pores are present in pneumonic lungs and in lungs in which edema has been produced mechanically but that they are not normal structures. In 1932 and 1937 he reaffirmed these convictions.

In 1927 Laguesse,[56] who also devoted many years to study of the lung, gave a general review of the discussions on the question of the alveolar pores. It will be recalled that in 1901, after having studied the lung for over twenty-six years, he was not convinced that interalveolar communications occurred normally in human lungs. But being impressed thereafter by the studies of Schulze,[41] he and his student set out (1911-1912) to settle the question of the pores to their own satisfaction. And, as he wrote, with new technics he was able to verify with all certitude the existence of pores in the lungs of mammals, including man. In his paper of 1927 Laguesse presented a drawing (fig. 4) of a 5 micron section of a human lung in which there are shown three perforated spaces or pores in the walls of one alveolus. In the same figure another pore is seen, which contains an isolated nucleated cell, labeled epithelial cell, half way engaged, making projections into each of the neighboring alveoli. In thin sections he has also noted pores occupied by free pigmented alveolar phagocytes which, in the process of passing through the walls, temporarily obliterate the openings.

Joannides [57] (1931) studied the structure of normal lungs of dogs and man in the living and fixed states with a stereomicroscope. In thick sections he frequently saw openings in the alveolar walls connecting adjacent alveoli. Zu Jeddeloh [58] (1931), in his study of normal and chronically congested human lungs, saw pores regularly in the alveolar walls of the normal specimens. Quite frequently he observed rounded *Epithelzellen* in the pores, with their cytoplasm extending into the adjacent alveoli.

Seemann [59] (1931) described interalveolar communications in the lungs of the mouse, rat, cat and guinea pig as having smooth sharp borders and being situated in the intercapillary spaces not occupied by the alveolar epithelium. He described a hyaline alveolar membrane as extending through the pores and becoming con-

55. Miller, W. S.: J. Exper. Med. **38**:707, 1923; **42**:779, 1925.

56. Laguesse, E.: Arch. per le sc. med. **51**:45, 1927.

57. Joannides, M.: Arch. Int. Med. **47**:19, 1931.

58. zu Jeddeloh, B.: Beitr. z. path. Anat. u. z. allg. Path. **86**:387, 1931.

59. Seemann, G.: Histobiologie der Lungenalveole, Jena, Gustav Fischer, 1931, p. 24.

tinuous with the membrane covering the adjacent side of the alveolar wall. Schulha [60] (1933) and Jeker [61] (1933) studied the changes in the lungs of some laboratory mammals in the late fetal and early postnatal periods by the silver nitrate method. Schulha concluded that the alveoli are lined by a continuous layer of flattened epithelial cells, a view held by Oppel and Miller. Jeker, however, on the basis of his studies, held to the classic view of Kölliker that the alveoli are lined by a membrane composed of nucleated cells and non-nucleated plates. In their illustrations both authors showed alveolar pores, Jeker in the lungs of a 5 day old and a 4 week old cat and Schulha in the lungs of a 5 month old cat.

From his studies of lobar pneumonia Loeschcke [62] (1931) concluded that one of the important avenues of spread of inflammatory exudate containing pneumococci is through the pores of Kohn. In this manner the inflammation may spread from lobule to lobule until the whole lobe is involved.

Brodersen [63] (1933) made tissue culture studies and studies of fixed and stained preparations of the lungs of the rat, mouse and rabbit. In the cultures of lung he observed large pigment-filled macrophages passing through the alveolar walls via the alveolar pores, and he presented three figures (6, 8 and 9) showing large phagocytes in some phase of passing through them. These findings were also noted by Bargmann [64] (1936) and Clara [65] (1936), who made extensive detailed microscopic studies of the finer structure of the alveolar walls in mammalian lungs.

Treutlein [66] (1902), Miller [67] (1904), Brandt [68] (1927) and Willis [69] (1933) emphasized the importance of the pores as an avenue for intra-alveolar spread of metastatic tumors. The pattern of the lung remains normal for a considerable distance into the interior of the enlarging tumor. The plugs of tumor occupying the alveoli are avascular, and the septums constitute the only stroma of the tumor. Willis presented two photomicrographs of metastases in the lung, one from carcinoma of the pharynx and one from sarcoma of bone. Each photograph shows the alveoli occupied by tumor plugs, which connect with one another at several points through the interalveolar openings.

Physiologic evidence of the interalveolar communications is brought out in the studies of Adams and Livingstone [70] (1931), Van Allen, Lindskog and Richter [71] (1931), Van Allen and Lindskog [72] (1931) and Lindskog and Van Allen [73]

60. Schulha, M.: Ztschr. f. Zellforsch. u. mikr. Anat. **17**:199, 1933.

61. Jeker, L.: Anat. Anz. **77**:65, 1933.

62. Loeschcke, H.: Beitr. z. path. Anat. u. z. allg. Path. **86**:201, 1931.

63. Brodersen, J.: Ztschr. f. mikr.-anat. Forsch. **32**:73, 1933.

64. Bargmann, W.: Die Lungenalveole, in von Möllendorff, W.: Handbuch der mikroscopische Anatomie des Menschen, Berlin, Julius Springer, 1936, vol. 5, pt. 3, p. 799.

65. Clara, M.: Ztschr. f. mikr.-anat. Forsch. **40**:147, 1936.

66. Treutlein, A.: Centralbl. f. allg. Path. u. path. Anat. **13**:520, 1902.

67. Milner, R.: Arch. f. klin. Chir. **74**:1078, 1904.

68. Brandt, M.: Virchows Arch. f. path. Anat. **264**:677, 1927.

69. Willis, R.: The Spread of Tumors in the Human Body, London, J. & A. Churchill, Ltd., 1933, p. 241.

70. Adams, W. E., and Livingstone, H. M.: Arch. Surg. **23**:500, 1931.

71. Van Allen, C. M.; Lindskog, G. E., and Richter, H. G.: J. Clin. Investigation **10**:559, 1931.

72. Van Allen, C. M., and Lindskog, G. E.: Surg., Gynec. & Obst. **53**:16, 1931.

73. Lindskog, G. E., and Van Allen, C. M.: Arch. Surg. **24**:204, 1931.

(1931). Adams and Livingstone [70] found that in producing obstructive pulmonary atelectasis in dogs complete obstruction of the main stem bronchus of the entire lobe was essential to the production of massive atelectasis, for complete obstruction of a secondary air passage of a part of a lobe was not accompanied by atelectasis of the obstructed part. In view of these experiments they concluded that there are peripheral interalveolar and interlobular communications through which air passes from the unobstructed portion of the lobe to prevent collapse of the obstructed part of the lung.

Van Allen and his co-workers studied this transfer of air and other substances between pulmonary lobules in the lungs of the dog, cat, rabbit, calf, pig and man. After inserting a cannula into one of the secondary bronchi of a lobe, they passed air, chloroform and ether under low pressure into the bronchus and its branches and found that it escaped through the peripheral portion of the tree into the surrounding lobules of the lung to return into the main stem bronchus. Similar experiments were carried out on living dogs, and the same results were obtained. Air passed with difficulty from lobule to lobule in the lungs of the pig and calf. They also reproduced the experiments of Adams and Livingstone and verified the results of these investigators. To study the interlobular passages these workers injected solution of methylene blue, india ink and suspensions of bismuth subnitrate crystals into secondary bronchi and followed the paths of these substances. They found that solutions of methylene blue passed readily from the lobules receiving the injections into the surrounding lobules through the collateral passages. The paths of the india ink and of the suspensions of bismuth subnitrate crystals were followed roentgenographically. It was observed that the india ink passed freely from the lobule receiving it through the collateral passages into the surrounding alveoli but that the larger bismuth crystals, being larger than the caliber of any of the openings, did not pass beyond the walls of the lobule receiving these crystals. They also noted that the transfer of air from lobule to lobule was prevented by the presence of large amounts of fluid in the air passages. To this phenomenon of the transfer of air from lobule to lobule directly through openings in the alveolar walls they applied the term "collateral respiration." Along with Adams and Livingstone they showed that it plays an important role in preventing focal pulmonary atelectasis.

Being stimulated by the recent controversy of various authors as to the nature of the alveolar lining in mammalian lungs, Josselyn [74] (1935) made a study of the lungs of young and old rabbits and guinea pigs, using old and modern histologic methods. He did not see pores in the expanded lungs of new-born guinea pigs but observed them regularly in thick stained sections of the lungs of young adult rabbits and guinea pigs, and more abundantly in the lungs of an old rabbit. They were more numerous in the lungs fixed by injection of the fixing solution through the trachea than in those fixed by injection through the blood vessels or those expanded and fixed by immersion in the fixing solution. The pores occurred so frequently in the lungs of a mink that approximately every intercapillary space was perforated. Josselyn's anatomic description agrees with those of earlier authors. He did not come to a definite conclusion as to whether the pores are normal structures but thought they appeared to result from the "continually recurring trauma incident to every day life, as well as from injury by necessary but perhaps over-violent methods of fixation." He pointed out that the "physiologic occurrence of pores in adult lungs and the readiness with which their numbers may be increased argue strongly against the existence of a continuous epithelium."

74. Josselyn, L. E.: Anat. Rec. **62**:147, 1935.

In 1929, after several years' study of the structure and dynamics of the bronchial tree, Macklin [75] joined with those who denied the presence of interalveolar openings in mammalian lungs. However, he became interested in the question of the pores as a result of the findings of Adams and Livingstone (1931) and Van Allen and his co-workers (1931) and again took up the study of the lungs with special reference to the occurrence of the interalveolar openings. He [76] made a histologic study of thick sections of the lungs of the adult dog, cat, rabbit, guinea pig and rat and of thirteen human subjects of both sexes, whose ages ranged from 2 years and 5 months to 82 years (1935 and 1936). He observed openings regularly in the septums of the lungs from all the specimens studied, and his description agrees with those of earlier authors. The pores were found to be larger and more numerous in the lungs of the older individuals and in different parts of the lung. He carried out experiments similar to those of Van Allen and co-workers on the lungs of man and of laboratory animals. He showed, as did Van Allen and his co-workers, that when a small bronchial subdivision receives an injection of air or liquid the territory directly affected fills first and then, if injection is continued, there is an overflow into the adjoining lobules until the entire lobe is filled. This finding was opposite to that reached by Miller,[19b] who performed similar experiments. Macklin was able to outline the limits of the lobules, "lobular frontiers," by adding to the injection fluid particles of bronze powder or lycopodium spores of a size too large to go through the pores. The larger particles accumulated at the peripheries of the filled lobules, which could be seen clearly, both grossly and microscopically. Microscopic observations of the lungs taken through the "frontier" of the territory receiving the injection showed that there were no lesions resulting from the transference of the air and liquids. There was no increase in the number of pores after the liquids were injected under low pressure. When two adjacent bronchial stems received injections of gelatin of different colors, each became surrounded by a region containing its own color, while the intermediate region showed a blending of hues, which was manifest in microscopic sections. On the basis of his anatomic and physiologic studies of the pores, or vents or fenestrae, as he preferred to call them, Macklin gave up his view of 1929 and recorded his conviction that the vents are normal openings and that they probably serve an important function.

Authors of the current textbooks of histology have commented very little on the subject of interalveolar openings in the lungs. However, the foreign authors Policard [77] (1935), Braus [78] (1934), Branca and Verne [79] (1934), von Möllendorf [80] (1933) and Sobotta [81] (1929) all present illustrations of pores in the alveolar walls and considered them normal structures. Of the American authors,

75. Macklin, C. C.: Physiol. Rev. **9**:1, 1929.

76. Macklin, C. C.: (*a*) J. Anat. **69**:188, 1935; (*b*) Arch. Path. **21**:202, 1936

77. Policard, A.: Précis d'histologie physiologique, ed. 3, Paris, Gaston Doin & Cie, 1935, p. 545.

78. Braus, H.: Anatomie des Menschen, Berlin, Julius Springer, 1934, vol. 2, p. 145.

79. Branca, A., and Verne, J.: Précis d'histologie, Paris, Masson & Cie, 1934, p. 501.

80. von Möllendorff, W.: Lehrbuch der Histologie, Jena, Gustav Fischer, 1933, p. 289.

81. Sobotta,[39] ed. 4, 1929, pt. 2, p. 118.

Bailey [82] (1936) accepted this view. Cowdry [83] (1934) and Jordan [84] (1934) accepted the view of Miller that the pores are artefacts. Maximow and Bloom [85] (1934) stated that the subject of the pores was still an open question but described the alveoli as thin-walled blind polyhedral sacs, opening only on that surface which faces the alveolar duct. Bremer [86] (1936) accepted the interalveolar openings in the septums as normal structures and stated his belief that they are lined by the alveolar epithelial membrane.

Authors of the current textbooks of pathology likewise have had little to say regarding the pores. Kaufmann [87] (1929) and Aschoff [88] (1936) included them in their brief description of the alveoli of the normal lung. Bell [89] (1934), Boyd [90] (1934), Karsner [91] (1935) and Delafield and Prudden [92] (1936) mentioned the openings in the septums only in connection with lobar pneumonia. MacCallum [93] (1936) said that they may be normal structures of the alveolar walls. The aforementioned authors of textbooks have all given one or more classic photomicrographs or drawings of fibrin strands extending across the alveolar walls in pneumonic lungs but have made no comment as to the possibility that the pores may act as avenues of intralobar spread of the infection.

COMMENT

Interalveolar communications have been described in the lungs of all varieties of adult mammals by a large group of competent workers. Their occurrence is so constant in mammalian lungs, including those of man, that one can hardly doubt their normal existence. They are seen in expanded normal lungs fixed and stained by all the common methods and in the lungs of both young and old animals.

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82. Elwyn, A., and Strong, O.: Bailey's Text-Book of Histology, ed. 9, Baltimore, William Wood & Company, 1936, p. 486.

83. Cowdry, E. V.: Textbook of Histology, Philadelphia, Lea & Febiger, 1934, p. 290.

84. Jordan, H. E.: Textbook of Histology, New York, D. Appleton-Century Company, Inc., 1934, p. 261.

85. Maximow, A., and Bloom, W.: Textbook of Histology, ed. 2, Philadelphia, W. B. Saunders Company, 1934, p. 440.

86. Bremer, J. L.: Textbook of Histology, ed. 5, Philadelphia, P. Blakiston's Son & Co., 1936, p. 322.

87. Kaufmann, E.: Pathology, translated by S. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, p. 388.

88. Aschoff, L.: Pathologische Anatomie, Jena, Gustav Fischer, 1936, vol. 2, p. 249.

89. Bell, E. T.: A Textbook of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1934, p. 525.

90. Boyd, W.: The Pathology of Internal Diseases, ed. 2, Philadelphia, Lea & Febiger, 1935, p. 151.

91. Karsner, H. T.: A Textbook of Human Pathology, ed. 4, Philadelphia, J. B. Lippincott Company, 1935, p. 569.

92. Delafield, F., and Prudden, T. M.: A Textbook of Pathology, revised by F. C. Wood, ed. 16, Baltimore, William Wood & Company, 1936, p. 695.

93. MacCallum, W. G.: A Textbook of Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1936, p. 526.

It is apparent after reading the various views on the subject of the alveolar pores that little has been added to the anatomic description of these pores in the last thirty years. They vary in size and shape according to the degree of expansion of the alveoli and the degree of filling of the blood capillaries. They are inconspicuous in the collapsed lung. When the capillaries are filled with blood or with some injection mass and the alveoli are moderately expanded, the pores appear as small round or oval canals which run at various angles through the septums.[94] They appear as elongated slits in the thinned septums when the alveoli are greatly expanded and the blood capillaries are collapsed.[95] The pores vary in diameter from 5 to 13 microns,[96] although Macklin described openings in the alveolar walls as large as half the width of the alveolar wall. In this study pores were seldom seen with diameters larger than the width of 2 red blood corpuscles. Since the studies of Russakoff [97] many workers have observed reticular fibers in the walls of the pores. Elastic fibers have also been described as completely encircling the openings.[98] Findings of the latter type were not observed in this study. Rather, the elastic fibers seemed partially to encircle the pores as they pursued a more or less straight course over the septums.[99]

The authors who consider the pores normal structures and who hold that the alveoli are lined by a continuous epithelial membrane composed either of nucleated cells and non-nucleated plates or of a continuous layer of flattened nucleated cells describe a separation of the nucleated cells or non-nucleated plates at the points where the pores perforate the walls.[100] Bremer,[46] on a theoretical basis rather than on actual observation, offers the view that the epithelial cells lining the alveoli also provide the lining membrane for the openings in the alveolar walls.

During the past twelve years an increasing number of workers have questioned the existence of a continuous epithelial membrane lining the pulmonary alveoli. Today the majority of workers hold that the nucleated cells which are scattered over the surfaces of the alveolar walls are isolated cells. Some consider them as of epithelial origin,[101] while

94. Hansemann.[26] Mueller.[42] Laguesse and Marchand.[44] Laguesse.[45] Marchand.[46]

95. Mueller.[42] Ogawa.[51] Josselyn.[74] Macklin.[76]

96. Laguesse and Marchand.[44] Marchand.[46] Laguesse.[45] Laguesse.[50]

97. Russakoff, A.: Beitr. z. path. Anat. u. z. allg. Path. **45**:476, 1909.

98. Nicolas.[36] Linser.[38] Macklin.[76a]

99. Hansemann.[30] Schulze.[41] Mueller.[42] Laguesse and Marchand.[44] Laguesse.[50] Marchand.[46]

100. Hansemann.[30] Schulze.[41] Mueller.[42]

101. Loreti, F.: Arch. ital. di anat. e di embriol. **36**:35, 1936. Seemann.[59] Bargmann.[64] Clara.[65]

others maintain that they are of a mesenchymal nature.[102] The majority of both groups of workers and others [103] accept the view that the membrane which covers the capillaries and intercapillary spaces is part of the connective tissue matrix of the alveolar walls. This membrane is smooth and can be followed without interruption into the pores, where it lines their walls.

In explaining the origin of the alveolar pores, the histologic structure of the mammalian lung at birth and its postnatal development must be considered. At birth the pulmonary alveoli are small, and their walls are wide. The interalveolar connective tissue is very cellular and so abundant in some septums that the capillaries are separated into two layers. The capillaries, fibers and connective tissue cells are in an amorphous ground matrix of mesenchymal origin. The epithelial cells in many areas no longer line the pulmonary alveoli in the form of a continuous membrane. Only a few remain as isolated cells in the intercapillary spaces. The lining membrane covering the capillaries is part of the connective tissue matrix.[104]

The lungs of rabbits, rats, cats and dogs have been studied at birth and early in the postnatal period. In these animals many of the intercapillary spaces in the alveolar walls at the time of birth and thereafter do not contain nucleated cells but are filled with the ground substance with its enclosed reticular and elastic fibers. These observations have been made by other workers.[105] It seems, then, that as growth takes place the alveoli enlarge as a result of repeated expansion and contraction of the alveolar walls during the normal act of respiration. This enlargement is due in part to the stretching and thinning of the alveolar walls and interlobular septums, which brings about gradual separation of the connective tissue cells and fibers in the interalveolar connective tissue stroma and reduces the alveolar membrane in the intercapillary spaces to a thin velum. This in the course of normal development of the lungs is resorbed, establishing communication between the alveoli of the same and neighboring lobules.[106]

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102. Lang, F. J.: Arch. f. exper. Zellforsch. **2**:93, 1926. Policard, A.: Bull. d. histol. appliq. a la physiol. **3**:236, 1926. Chiodi, V.: ibid. **8**:61, 1931. Renaut.[35] Josselyn.[74]

103. Loosli, C. G.: Anat. Rec. **62**:381, 1935. Bratianu, S., and Anghelesco, G.: Arch. d'anat. micr. **28**:236, 1932.

104. Clara.[65] Josselyn.[74] Loreti.[101]

105. Costa, A.: Sperimentale, Arch. di biol. **86**:505, 1932. Alice, C.: Monitore zool. ital. (supp.) **43**:323, 1933. Galli, R.: Arch. ital. di anat. e di embriol. **34**: 277, 1935. Seemann.[59] Clara.[65] Josselyn.[74]

106. Spadolini, I.: Arch. ital. di anat. e di embriol. **14**:315, 1915-1916.

Laguesse [56] said that the phenomenon of resorption assists the normal functional repeated extensions and retractions of the alveolar walls in producing the perforations. He also asserted that there exists a hereditary tendency for the pores to form in the alveolar walls at a given time since one cannot indefinitely retard them, as shown by Caradonna's [47] experiments, and since they show themselves ordinarily in very young animals. The fact that the pores are of constant occurrence in the walls of normal lungs seems to be further evidence that the lining membrane of the alveoli is of mesenchymal origin, for it is hard to conceive how a greatly thinned epithelial membrane could survive the trauma, desquamation or retraction necessary to produce such persistently occurring openings without showing some evidence of its regenerative activity.

In the normal adult lung the wall of an alveolus is composed of a network of closely set blood capillaries, which are supported in the meshes of the reticular and elastic fiber networks. Accompanying the connective tissue fibers are a few connective tissue cells (fibroblasts and fixed tissue histiocytes). The capillaries, reticular and elastic fibers and connective tissue cells are enclosed in an amorphous ground membrane of mesenchymal origin. This membrane forms the lining of the alveolar spaces [107] and in some intercapillary spaces it is interrupted to form direct passageways between adjacent alveoli. Scattered over the alveolar surfaces are single nucleated cells which may be of endodermal or mesodermal origin.[108]

Robertson and his co-workers [109] have shown clearly that the isolated nucleated cells of the alveolar walls hypertrophy, desquamate and become free alveolar macrophages during the course of experimental pneumonia in dogs and lobar pneumonia in man. They make no distinction between cells of mesenchymal or endodermal origin in and on the alveolar walls but designate the local response on the part of these cells to the infection as the "macrophage reaction."

The evidence on which Miller bases his view that the pores are not normally occurring structures in the alveolar walls is not sufficient to warrant such wide acceptance. Miller [19] saw no interalveolar openings in the reconstruction preparations of the lungs of various mammals. The reason for this was not that openings were absent from the alveolar walls, but that he used too thick (20 micron) sections of lungs in making his reconstructions. Laguesse and Marchand [110] made careful

107. Clara.[65] Josseyln.[74] Loreti.[101] Loosli.[102]

108. Bargmann.[64] Clara.[65] Josselyn.[74] Lang.[102]

109. Robertson, O. H.; Coggeshall, L. T., and Terrell, E. E.: J. Clin. Investigation **12**:433, 1933. Robertson, O. H., and Uhley, C. G.: ibid. **15**:115. 1936.

110. Laguesse and Marchand.[44] Marchand.[40b] Laguesse.[56]

measurements of the diameters of the pores in the lungs of man and various laboratory animals and found that only rarely did they reach a diameter of 13 microns. For Miller to have found pores in his reconstruction preparations it would have been necessary that he cut the lung sections much thinner than he did, i. e., thin enough (5 microns) so that they would appear as complete interruptions in the alveolar walls.[50]

The contention by Miller [55] that the epithelial cells must be pushed off diametrically opposed surfaces of an alveolar wall before a pore is formed is not supported in experimental lobar pneumonia in dogs and monkeys. The alveolar pores are seen in the lungs of normal animals and also in those of animals killed during all stages of the infection. In the early lesions the openings contain fibrin, which extends from one alveolus to another, before there are local hypertrophy and desquamation of cells from the walls. The pores are present in the septums when the local reaction of the alveolar walls is at its height and are also seen in lungs completely recovered from the infection. Because the pores in the alveolar walls of pneumonic lungs contain fibrin and cells, they are more conspicuous than in thin sections of normal lungs. For this reason, a pathologic origin has been mistakenly assigned to them.

Furthermore, it is not necessary to resort to pathologic specimens or inflammatory processes to demonstrate their presence in thin sections as has been necessary in the case of the so-called alveolar epithelium. This picture of strands of fibrin passing through the alveolar walls can be easily produced in normal lungs by injecting heparinized plasma into the lungs of healthy animals and allowing it to clot. Stained sections of such lungs show even more clearly than is seen in pneumonic lungs the fibrin network passing through a varying number of openings in the alveolar walls. This experiment gives further evidence that the openings in the alveolar walls were present before the plasma was injected into the lungs and were not dependent on the desquamation of cells from the surfaces of the alveolar walls as Miller maintained. It also supports and emphasizes the importance of Hansemann's [26] injection experiments made forty-two years ago. The injected gelatin in the lungs which Hansemann [26] described passed, in all probability, through the pores, rather than diffused through the walls, as Miller contended.

Some authors have associated the alveolar pores with pulmonary emphysema.[111] Macklin [76b] stated that if the pores are to be regarded as evidences of emphysema this condition is in its broader sense almost universal in the lungs of mammals and is present in the young as well

111. Letulle, M.: Arch. méd.-chir. de l'app. respir. **3**:89, 1928. von Ebner.[27] Linser.[38]

as in the old. Because these perforations form early and persist as such without being appreciably increased with age, Laguesse [56] cannot associate them with the beginning of emphysema and consequently a pathologic phenomenon. He further pointed out that the presence of minute orifices in the septums permitting a certain equilibrium of pressure between two neighboring alveoli would tend to prevent emphysema rather than to favor its formation. Orsos [112] has shown that the initial lesion in emphysema is the enlargement and subsequently the disappearance of the capillary loops and pericapillary elastic and connective tissue fibers. The alveolar wall then breaks and openings are formed which become enlarged and converge with others to produce still larger holes of emphysematous character. Other workers [113] also have expressed the view that the part played by the pores at the beginning of pulmonary emphysema is overemphasized, for in specimens of normal lungs in which pores are abundant no evidence of a breakdown of the elastic fibers and capillary networks is encountered.

In normal lungs the interalveolar and interlobular openings may be looked on as collateral air passages for the equalization of the intra-alveolar pressure which tend to prevent focal pulmonary atelectasis when secondary bronchi become temporarily or permanently obstructed.[114] The finding of large pigment-filled free alveolar phagocytes in the pores in fixed and stained preparations suggests that these openings also serve as a passageway by which free cells migrate from one alveolus to another.

In this study of experimental pneumococcic pneumonia in dogs and monkeys which received survival doses of pneumococci, the great majority of the organisms in the spreading lesions were seen in the bronchial, bronchiolar, alveolar duct and alveolar spaces rather than in the substance of the alveolar walls or in the lymphatic and blood capillary spaces. Pneumococci were also frequently seen free and in cells in the interalveolar openings. These findings strongly indicate that the primary lesion begins in the terminal air passages and that they along with the alveolar pores are the most important avenues by which the edema fluid, cellular exudate and infecting organisms spread throughout the involved lobes. Gunn and Nungester [115] described this mechanism of intralobar spread in experimental pneumonia in rats. In pneumococcic lobar pneumonia in man, the air passages and openings in the alveolar walls serve a similar capacity.[62] From these observations one must conclude that the pores provide avenues of spread for other

112. Orsos, F.: Beitr. z. path. Anat. u. z. allg. Path. **41**:95, 1907; Beitr. z. Klin. d. Tuberk. **87**:568, 1936.

113. Hansemann.[26] Sudsuki.[29] Macklin.[76b]

114. Laguesse.[56] Adams and Livingstone.[70] Lindskog and Van Allen.[73]

115. Gunn, F. D., and Nungester, W. J.: Arch. Path. **21**:813, 1936.

types of infection (tuberculosis) which produce exudative lesions in the lungs. Macklin [76b] also asserted that they must be considered in the mechanism of intralobar spread of fluid in pulmonary edema.

Primary and secondary carcinoma and sarcoma may utilize the pores to grow from alveolus to alveolus without injuring the alveolar walls from which they get their food supply.[116]

SUMMARY

This study and those of others show that the pores are normal constituents of the alveolar walls in the lungs of a wide variety of mammals including man. Their presence in the alveolar walls gives support to the view that the lining membrane is of mesenchymal origin. They are not formed as a result of inflammatory processes but are only more frequently noted in thin sections of pathologic lungs, especially pneumonia, because they contain fibrin and cells. When studying the normal mechanism of respiration the pores must be taken into consideration. In pathologic lungs they provide one of the important passageways by which infections and tumor growths spread throughout the involved lobes.

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116. Treutlein.[66] Brandt.[68] Willis.[69]

CONGENITAL ATRESIA OF THE TRICUSPID VALVE

COMPLICATED BY CONGENITAL MYXOSARCOMA OF THE LABIUM MAJUS

ARTHUR L. AMOLSCH, M.D.
DETROIT

Congenital atresia of the tricuspid orifice is one of the more rare cardiac malformations and presents a triad of concomitant defects peculiar to it, namely, complete absence of the orifice and structures of the tricuspid valve, patency of the foramen ovale and a defect in the upper part of the interventricular septum.

Physiologically, this situation is characterized by hypertrophy of the left ventricle, with left ventricular preponderance shown on the electrocardiographic tracing, and by a murmur in the second to third intercostal space, near the left border of the sternum. The evidence of inadequate pulmonary oxygenation and circulation is manifest in cyanosis, which in some instances is constant from birth, but frequently is of a minor degree after birth, progressing in severity, and often characterized by recurrent attacks, tending to become more severe. The subjects who survive sufficiently long come to have pulmonary arthropathy, and some exhibit compensatory polycythemia.

The patient under consideration presented an additional feature of interest in that another defect in the development and growth of mesenchymal tissue was exhibited in a congenital tumor of the left labium majus, which increased rapidly in size and ultimately resulted in a second subcutaneous tumor on the back and multiple small tumors in both lungs. These secondary growths had histologic features identical with those of the original tumor.

REPORT OF CASE

The patient, a white girl, was born Dec. 13, 1936. The mother was normal in all respects. At birth the infant showed no unusual cyanosis, and respiration was quickly established. There was noted a tumorous swelling in the left labium majus, extending into the inguinal area. This mass was rather firm; it was trilobate in outline and suggested inguinal hernia or possibly hermaphroditic organs. It progressively increased in size until, within ten days, the overlying skin was rather tense and bluish red. The adjacent superficial veins were larger and somewhat tortuous. Within one month the tumor had attained a size three times greater than at birth, and the overlying cyanosis was more prominent. The

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tumor was dissected out and was found to be multilobulated, encapsulated, fairly firm in consistency but rather myxomatous, and bluish red. Microscopic examination showed this growth to be myxosarcoma of low malignancy. The incision healed nicely, and there was no local recurrence.

March 9, 1937, when the infant was nearly 3 months old, intermittent attacks of cyanosis developed in association with coldness and clamminess of the extremities. The infant had been gaining in weight satisfactorily. The respiratory rate was increased to from 40 to 60. An x-ray film of the thorax suggested that the thymus gland was enlarged, since the mediastinal shadow was widened. Radiation therapy was instituted but had no effect on the cyanosis. The attendant noted that the infant cried before each attack. At this time a loud systolic murmur was heard for the first time over the entire precordium, attaining its maximum intensity at the third intercostal space near the left border of the sternum. April 11, a small tumor nodule, freely movable, was noted in the subcutaneous tissue of the posterior wall of the chest, just below the scapula. This growth increased in size and was removed April 22. It was easily removed from its position and presented as a somewhat flattened tumor, 1.5 cm. in diameter, which was distinctly myxomatous. Microscopic examination showed it to be a well vascularized, loosely assembled growth of stellate and spindle cells, with very few mitotic nuclear forms present. By April 15 the cyanosis was marked, and the attacks were more frequent. April 20 the temperature rose to 104 F. There was slight cough, which exaggerated the cyanosis. Occasional râles were heard in both pulmonary fields posteriorly. April 27 the infant exhibited muscular twitching of the hands, which were held rigid. Convulsive movements occurred at intervals of from fifteen to forty-five minutes. The terminal temperature was 108 F., the infant dying April 27.

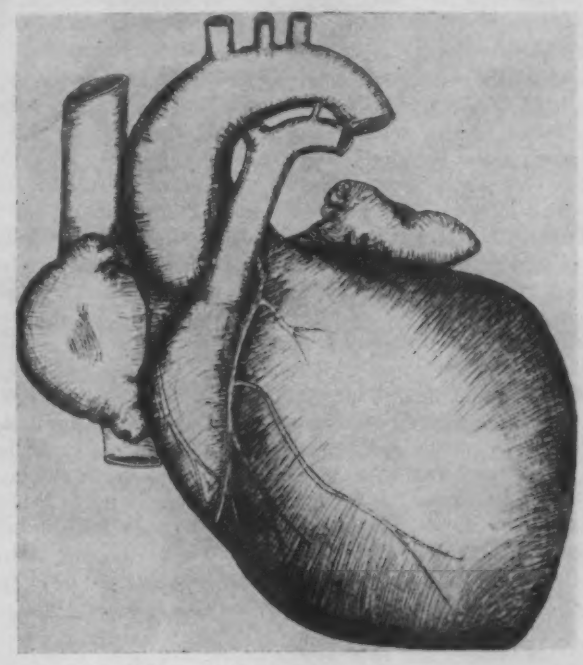
Observations at Autopsy.—The subject was a white girl 4 months old. There was no external malformation. The general nutrition was excellent. The cutaneous surface showed no cyanotic discoloration. The left inguinal wound was well healed and showed but slight induration. No palpable recurrence of the tumor was present. A recent small operative incision below the angle of the left scapula was ununited.

There was no transudate or exudate in the pleural spaces. The left lung was normally developed; it was well expanded and appeared hyperventilated. Only slight hypostatic congestion was evident. The right lung showed abnormal division into lobes, the interlobar septums being incomplete on the surface. The lung in areas showed the mottled reddish blue discoloration of early bronchial pneumonia. Each lung showed from five to six small flat light pink plaques, which were slightly elevated above the general pleural surface. These could barely be palpated and were seen clearly only with reflected light. They grossly suggested endotheliomatous tumors. They were present on all visceral pleural surfaces, while the parietal pleura was not so involved. The largest of these tumors measured 4 mm. in surface diameter, and they were from 0.5 to 2 mm. in depth. Close examination revealed that each nodule was limited within the confines of the surface lobular outlines. No nodularity could be seen or palpated in the lung parenchyma.

The areolar tissue of the upper part of the anterior mediastinum exhibited a reddish blue lentil-shaped node 4 mm. in diameter. Grossly, this was thought to be a lymph node, but microscopic examination proved it to be a tumor of a character identical with that of the nodules found in the lungs. Mediastinal and hilar lymph nodes were slightly enlarged and hyperemic.

The thymus was diminished to about half normal size and was dark bluish red.

The pericardial sac contained no excess of fluid and was entirely normal. The heart was definitely enlarged, the ventricular portion consisting largely of a hypertrophied left ventricle. The heart, including the pulmonary and aortic vessels, weighed 44.5 Gm. Its greatest transverse diameter was 4.5 cm. Its length was 4.2 cm. The right ventricle was markedly hypoplastic, measuring 2.6 cm. in length and 1 cm. in width, and its chamber was 3 mm. in depth. It appeared to consist largely of bulbus pulmonis. The circumference of the pulmonary valve orifice measured 1.4 cm. The valve was equipped with three equal-sized, normal-appearing leaflets. The aortic valve orifice had a circumference of 2.2 cm., and three normal leaflets were present. The coronary orifices were normally situated. There was no transposition of the great vessels. The pulmonary artery was



Semidiagrammatic drawing of the heart showing atresia of the tricuspid valve; × 2.

hypoplastic, its diameter being about half that of the aorta, which in its ascending portion and arch had a diameter of 1.5 cm. The ductus Botalli was represented by a 1 mm. nonpatent cord. The wall of the left ventricle averaged 1.1 cm. in thickness. The mitral valve consisted of two cusps, and the anteromedian part of the valve was slightly thickened. Its orifice had a circumference of 3 cm. The right auricle was large and rather quadrate, and its chamber was dilated. Its anterolateral wall had a thickness of from 2 to 6 mm. The relationship of the superior and inferior vena cava was normal. There was no vestige of the orifice or structures of the tricuspid valve. The foramen ovale was patent to a diameter of 0.8 mm. and was provided with a membranous valve (septum secundum) which practically spanned the foramen when not under tension.

The upper part of the interventricular septum had a defect 2 mm. in diameter, which was directed slightly upward and to the right from the chamber of the left ventricle.

The peritoneal cavity contained no free fluid or exudate. The liver was enlarged and exhibited passive congestion. Its cut surface showed distinct, sharply defined degeneration, central in each lobule. The spleen was enlarged to three times normal size; it was firm in consistency and dark red. All other abdominal organs were normal except for passive congestion.

The superior longitudinal sinus and its emergent veins were thrombosed, the thrombus being mixed red and white. There was extensive subarachnoid hemorrhage, especially marked over the left cerebral hemisphere. The accumulated blood widened the sulci to 1 cm. There was marked congestion of the cerebral cortex with extravasation hemorrhage and early softening in the rolandic area on both sides. There was no other intracranial pathologic change.

Microscopically, the congenital tumor of the labium majus was very vascular and quite cellular in areas, the intervascular cells being of the stellate and the spindle type, with areas of myxomatous stroma. Cell division was moderately active, but there was no prominent anaplasia. Irregular areas of central necrosis were present. This tumor was interpreted as a myxosarcoma of relatively low malignancy. The second tumor, removed from the scapular region, was grossly semitranslucent and slippery to the touch; microscopically, it consisted of a loose mesh of spindle and stellate cells with a rather rich vascular bed. Mitoses were not noted in this tumor. However, there was evidence that skeletal muscle fibers were included in it, indicating invasive capacity. The mediastinal tumor was essentially identical in structure with the second biopsy tissue. The subpleural nodules in the lungs were well vascularized, and their histologic structure was identical with that of the subcutaneous and mediastinal growths. However, the capacity to invade partially the thin-walled blood vessels, with occasional formation of a polypus-like growth within the lumen of a blood vessel, and the undoubted capacity to invade the stroma of the pulmonary alveolar walls, so that lung parenchyma was enclosed in the substance of the tumors, were indicative of the malignant nature of these growths. Moreover, isolated microscopic neoplastic nodules of an identical type of tissue were found deep in the lung parenchyma.

COMMENT

This case is one of the few of tricuspid atresia in which progressive repeated attacks of severe circulatory incompetence resulted in right auricular hypertrophy and dilatation leading to venous stagnation, thrombosis of the superior longitudinal sinus and subarachnoid hemorrhage as the terminal picture.

Clinically there were exhibited in this case an increased respiratory rate of from 40 to 60 and a red blood cell count of 5,500,000, indicating some compensatory polycythemia. In Wieland's case [1] polycythemia was more pronounced.

The x-ray films of the thorax were studied by several competent roentgenologists, who estimated that the area of cardiac opacity was within normal limits for the age. It is obvious that in cases in which

1. Wieland, E.: Jahrb. f. Kinderh. **79**:320, 1914.

the ventricular portion of the heart consists largely of the left ventricle the area of cardiac opacity may be within normal limits and offer difficulties in recognition of the pathologic condition.

Congenital atresia of the tricuspid orifice has been classified by Wieland [1] into a primary type, with which there coexists no other cardiac maldevelopment, and a complicated type, with which other cardiac malformations do exist. There is reasonable justification on embryologic grounds for the separation of cases into these two groups, particularly as regards the primary form, since the development of the septum between the auricles and the fusion of this septum with the endocardial cushions of the primitive atrioventricular orifice occur during the third and fourth weeks of fetal life. If overgrowth and fusion of the endocardial cushions to the right of the interatrial septum occur during this developmental period, atresia of the tricuspid orifice will result. The two associated abnormal communications between the auricles and ventricles then result as matters of necessity and are an essential part of the pathologic picture.

Vierordt [2] suggested that an unequal division of the primitive atrium by a septum developing too far to the right causes tricuspid atresia. As the septum fuses with the cushions, it seals over the right atrioventricular orifice. This explanation is accepted by Wieland [1] and Mönckeberg.[3] Kühne [4] explained the atresia in a different manner, stating that in early fetal life the septum primum is normally directed toward the right margin of the single atrioventricular orifice, but as the atrioventricular canal also normally shifts from left to right, the free margin of the septum comes to meet the lips of the orifice in the middle. When this shift from left to right fails, there results stenosis or atresia of the tricuspid orifice. Support for this theory is given by the knowledge that congenital atresia of the mitral valve is the rarest of all atresias of cardiac orifices.

In a strict sense, the acceptance of a pure or primary tricuspid atresia is largely academic, since this anomaly represents a degree of pathologic deviation. In the majority of cases of tricuspid atresia there is exhibited some degree of hypoplasia of the pulmonary artery, which in part may represent unequal division of the conus arteriosus. In two cases (Aschoff and Schreiber;[5] Breslich [6]) there were but two semi-

2. Vierordt, H.: Primäre Fehler am Osteum venosum dextrum, in Nothnagel, C. W. H.: Spezielle Pathologie und Therapie, Vienna, A. Hölder, 1901, vol. 15, pt. 2, p. 197.

3. Mönckeberg, J. G.: Die Missbildungen des Herzens, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, pt. 1.

4. Kühne, M.: Jahrb. f. Kinderh. **63**:235, 1906.

5. Aschoff and Schreiber: Deutsche med. Wchnschr., supp. 8, 1901, p. 63.

6. Breslich, P. J.: Arch. Path. **10**:206, 1930.

Tabulation of Cases of Atresia of the Tricuspid Valve

Author	Date	Sex	Age	Primary	Complicated	Type of Complication	Evidence of Endocarditis
Rauchfuss [10]							
Kreysig	1817	M	7 days	..	+	Transposition of arteries	
Vrolik	....	M	9 yrs.	..	+	Rudimentary ventricular septum	
Nuhn	....	M	6 wks.	+	..		
Valleix	....	M	8 days	..	+	Transposition of venae cavae; rudimentary ventricular septum	
Peacock	....	..	8 yrs.	+	..		
Kühne [4]							
Kühne	1906	..	7 mos.	+	..		
Kühne	1906	..	9 mos.	+	..		
Burdack	....	M	27 yrs.	+	..	.....	Endocarditis
Hiffe	....	..	4 mos.	+	..		
Henriette	....	..	5 yrs.	+	..	.....	Endocarditis
Chapotot	1880	F	20 mos.	+	..		
Kelly	1866	..	5 mos.	+	..	Rudiments of tricuspid valve	
Abercrombie [7]	1882	F	5 mos.	..	+	Pulmonary stenosis	
Vierordt [3]							
Gelpke	1883	..	27 yrs.	..	+		
Klug	....	F	10 mos.	..	+	Synechia of pulmonary valve	Endocarditis ?
Dobner	....	..	10 yrs.	..	..	.....	Endocarditis
Barlow	....	..	12 wks.	..	..	.....	Endocarditis
Schuberg	....	..	12 mos.	..	..	.....	Induration about septal defect
Ferber	....	..	12 mos.	..	..	.....	Endocarditis
Favell	....	..	10 yrs.	..	+		
Holmes	....	..	22 yrs.	..	+		
Schipmann [12]	1869						
Krabbe [15]	1864						
Aschoff and Schreiber [5]	1901	M	30 mos.	..	+	Two semilunar cusps to pulmonary valve	
Bernstein [11]	1906	..	32 mos.	..	+	Four branches from aorite arch	Vegetation on septal defect
Wieland [1] and Sieveking	1914	F	4 mos.	+	..		
	1854	..	2 mos.	+	..		
Hedinger, E.: Centralbl. f. allg. Path. u. path. Anat. **26**: 529, 1915	1915	F	56 yrs.	..	+	Transposition of arteries	
Hess, J. H.: Am. J. Dis. Child. **13**: 167, 1917	1917	..	9 mos.	+	..		
Basel Pathological Institute	....	..	58 yrs.	..	+		
Huebschmann [13]	1921	..	5 mos.	..	+	Double vena cava superior; 4 leaflets on aorta; 4 mitral papillary muscles	
Huebschmann [13]	1921	..	6 mos.	..	+	Ductus Botalli to innominate artery	
Mönckeberg [9]	1924	..	.....	+	..		
Rihl, J.; Terplan, K., and Weiss, F.: Med. Klin. **25**: 1543, 1929	1929	..	7 mos.	+	..		
Breslich [6]	1930	M	8 mos.	..	+	Two pulmonary leaflets	

Tabulation of Cases of Atresia of the Tricuspid Valve—Continued

Author	Date	Sex	Age	Primary	Complicated	Type of Complication	Evidence of Endocarditis
Papillon, P. H., and Mourrut, E.: Bull. Soc. de pédiat. de Paris **29**: 503, 1931	1931	..	5 mos.	+	..	Ectopic cordis	
Cassoute; Poinso, R., and Morel: Marseilles méd. **2**: 306, 1931	1931	..	5 mos.	..	+	Transposition of arteries	
Murphy, G. R., and Bleyer, L. E.: Am. J. Dis. Child. **46**: 350, 1933	1933	M	4 mos.	+	..		
Billet, S., and Stewart, H. L.: Am. J. Dis. Child. **45**: 1247, 1933	1933	F	42 mos.	+	..		
Wason, I.: J. Tech. Methods **13**: 106, 1934	1934	F	5 mos.	..	+	Transposition of arteries	
Grayzel, D. M., and Tennant, R.: Am. J. Path. **10**: 791, 1934	1934	..	10 hrs.	+	..	Coronaries arising from pulmonary artery	
Terplan and Sanes [14] Prague Pathological Institute	1936						
Taussig [8]	1936	..	.....	..	+	Pulmonary stenosis	
Amolsch	1937	F	5 mos.	+	..		
Beaver	....	..	3 mos.	+	..		

lunar cusps to the pulmonary valve. In two other cases (Abercrombie;[7] Taussig[8]) there was pulmonary stenosis, again indicating unequal separation of the conus arteriosus.

Abbott[9] listed a total of twenty-five cases of tricuspid atresia, which she classified as follows: sixteen primary and nine complicated. It is difficult to determine accurately the reported incidence in both classes since many of the references to cases by the earlier authors were not accompanied by suitable references to the literature.

Rauchfuss[10] in 1878 made the first attempt to group cases of atresia of a purely developmental nature and accepted five from the literature. Kühne[4] in 1906, making a similar review, accepted six cases reported prior to that time; however, but one of these was listed by Rauchfuss; specifically, the case described by Nuhn.

It seems desirable at this time to tabulate a complete list of the reported cases of congenital atresia of the tricuspid orifice, with references as complete as possible. An attempt is made to classify them according to the criteria recommended by Wieland.[1] At the present time there are recorded nineteen instances of primary tricuspid atresia, including the case herein described. One additional unreported case has been observed in Detroit by Dr. D. C. Beaver. A second group of

7. Abercrombie, J.: Tr. Path. Soc. London **34**:78, 1882-1883.

8. Taussig, H. B.: J. Tech. Methods **16**:66, 1936.

9. Abbott, M.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936.

10. Rauchfuss, C.: Die Krankheiten der Kreislauforgane, in Gerhardt, C.: Handbuch der Kinderkrankheiten, Tübingen, H. Laupp, 1878, vol. 4, pt. 1, pp. 99-107.

eighteen cases, classified as complicated, are recorded. Three cases are unclassified, and in four cases the condition was attributed by Vierordt to endocarditis. The total group of known cases now numbers forty-five.

It is to be noted that among the cases of complicated atresia evidence of endocarditis was exhibited in three, namely, the case of Klug, the case of Bernstein [11] and the second case described by Huebschmann.[12] Included among the cases of primary atresia listed by Kühne there are two in which the condition was considered by Rauchfuss to have an inflammatory basis, namely, the Burdach and Henriette cases. Three cases included in the accompanying table have been left unclassified because of inability to gain access to the original case reports. These are the cases of Schipmann,[13] the case in the Prague Pathological Institute referred to by Terplan and Sanes [14] and Krabbe's [15] case.

The problem of determining the influence of fetal endocarditis in the production of tricuspid atresia is difficult. To be completely explanatory the inflammatory damage must have been accomplished during the third and fourth weeks of embryonic life and must have resulted in hypoplasia of the right ventricle and persistence of the interauricular and interventricular communications. In instances in which the duration of life has been long it is difficult to determine whether the endocarditis may not have been superimposed on areas of primary defective development. In some instances it is impossible to say that developmental stenosis has not terminated in inflammatory atresia.

The existence of a large defect in the interventricular septum, transposition of the arterial trunks and other compensating vascular communications may be compatible with a relatively long life expectancy.

Since several of the cases, like that reported here, have not been indicated in early cyanosis, it is possible that the small interventricular communication was sufficient for the small needs in the postnatal period but became incompetent because of hypertrophy of the ventricular wall and because the physiologic requirements increased.

SUMMARY

A case of primary congenital atresia of the tricuspid valve is reported. The association of congenital myxosarcoma of the left labium majus and inguinal region, resulting in metastases to the lungs during the four months of postnatal life, attaches additional interest to this case in that the case illustrates two types of developmental and growth defect.

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11. Bernstein, E. P.: Proc. New York Path. Soc. **6-7**:29, 1906-1908.
12. Huebschmann, P.: Verhandl. d. deutsch. path. Gesellsch. **18**:174, 1921.
13. Schipmann, D. G.: Ueber angeborne Stenose oder Atresie des Ostium atrio-ventriculare dextrum, Jena, A. Neuenhahn, 1869.
14. Terplan, K., and Sanes, S.: J. Tech. Methods **15**:86, 1936.
15. Krabbe, H.: Hospitalstid. **7**:149, 1864.

The clinical exhibition of intermittent cyanosis and dyspnea of mild degree immediately after birth, but increasing in severity and frequency of attack after the second month, is recorded in many of the reported cases. The increased respiratory rate and the slight polycythemia exhibited in this case are noted at times in various forms of congenital heart disease.

The evidence of cardiac enlargement to the left, the dilated right auricle and the systolic murmur audible in the third month and having its maximum intensity in the third intercostal space near the left border of the sternum are typical of the findings in many of the cases.

The rapidly progressive overloading of the right auricle, with terminal thrombosis of the superior longitudinal dural sinus and subarachnoid hemorrhage over the vertex of the cerebrum, is an unusual complication.

A tabulation of recorded cases of congenital atresia of the tricuspid valve of primary and complicated types is presented.

Case Reports

GANGLIONEUROMA OF THE VERMIFORM APPENDIX

Histologic Study of a Case

BEN W. LICHTENSTEIN, M.D., AND ALEX B. RAGINS, M.D., CHICAGO

Of the great variety of tumors found in the vermiform appendix, a true neuroma containing large numbers of ganglion cells is only rarely seen. This type of neurogenic tumor, though generally rare, is common in the sympathetic nervous system and of less frequent occurrence in the cerebrospinal nerves and their ganglions, the brain and the spinal cord. In one instance, reported by Poate and Inglis,[1] such a tumor was located in the intestine, and in Oberndorfer's [2] case the neoplasm was present diffusely throughout the wall of the appendix in the form of so-called ganglioneuromatosis, associated with partial primary giant growth of that organ.

Virchow [3] was the first to differentiate satisfactorily the true neuroma, containing newly formed nerve elements, from the false neuroma, in which such elements were absent. Pick and Bielschowsky [4] classified the true neuroma on an embryologic basis. They stated that all true nerve tumors are the result of a defect in embryonal development in which there is an abnormal deposition of multipotential neurocytes. By the differentiation or lack of differentiation of these cells mature or immature forms of neuroma arise. Whereas, to the latter group belong such growths as the malignant neurocytoma and sympathicoblastoma, to the former belongs the benign ganglioneuroma, in which the multipotential cell has matured and differentiated in the direction of the ganglion cell.

Such a tumor rich in ganglion cells was present in the vermiform appendix in our case, which clinically produced the picture of acute appendicitis.

REPORT OF CASE

A colored girl aged 8 years was admitted to the children's surgical ward of the Cook County Hospital, March 1, 1937, with the diagnosis of acute appendicitis. She stated that she was perfectly well until 8:00 a. m. February 27, when she was seized with a sudden severe cramplike pain in the abdomen, which at first was diffuse but later became localized to the right lower quadrant. Shortly afterward she became nauseated and vomited. The nausea and the pain in the right lower quadrant continued throughout the next day, and she vomited whenever she ate anything. She entered the hospital after an illness of sixty-four hours.

From the Department of Pathology of the Cook County Hospital; Dr. R. H. Jaffé, director.

1. Poate, H., and Inglis, K.: Brit. J. Surg. **16**:221, 1928.

2. Oberndorfer: Ztschr. f. d. ges. Neurol. u. Psychiat. **72**:105, 1921.

3. Virchow, R.: Virchows Arch. f. path. Anat. **13**:256, 1858.

4. Pick, L., and Bielschowsky, M.: Ztschr. f. d. ges. Neurol. u. Psychiat. **6**:392, 1911.

She was well nourished and well developed, not acutely ill but complaining of pain. The rectal temperature was 102 F., the pulse rate 90 and the respiration rate 20. The pharynx was slightly injected, and the teeth were carious. Examination of the heart and lungs showed nothing of importance. Palpation of the abdomen revealed mild rigidity and tenderness in the right upper and lower quadrants. The liver, kidneys and spleen were not palpable, and on auscultation

Fig. 1.—Low power photomicrograph of the mucosal layer of the vermiform appendix showing a separation of the glands by an increase in the stroma, which is rich in ganglion cells; Van Gieson's stain; × 150.

peristaltic sounds were heard. Rebound tenderness was elicited over the right lower quadrant. The extremities as well as the genitalia were essentially normal. There was leukocytosis (16,000); vaginal smears were negative for gonococci.

The diagnosis was acute appendicitis. At operation the appendix was found behind the cecum, and its tips pointed toward the umbilicus. Its serosa was moderately injected. No other intra-abdominal changes were found.

Pathologic Examination.—The appendix measured 6.5 cm. in length and 0.5 cm. in the greatest diameter. The serosa was deeply injected, dull and granular. The wall measured 2 mm. in thickness, and the mucosa was light tan-gray, mottled with areas of purple-red. In the distal third of the appendix a pedunculated soft node, measuring 4 by 2 mm. in diameter and attached to the mucosa by a pedicle 4 mm. in diameter, protruded into the lumen. Sections were taken from the region of this polyp. The mucosa was composed of regularly placed normal-

Fig. 2.—High power photomicrograph showing large ganglion cells with distinct Nissl substance, surrounded by a variety of cells (see text for details); Mallory's phosphotungstic acid-hematoxylin stain; × 500.

appearing glands lined by a layer of high columnar, mucus-producing epithelium. The muscularis mucosae, as well as the submucosa and the muscularis propria, was unchanged. At one point the mucosa was greatly thickened and thrown upward, with the submucosa, into the lumen of the appendix in the form of a fold. In this region the glands were widely separated by a diffusely increased stroma. The increase in the stroma was confined to the mucosa and was due to an accumulation of numerous elongated, spindle-shaped cells and larger irregularly shaped cells

arranged singly or in clusters, in addition to the fibrocytes, lymphocytes and occasional eosinophilic leukocytes normally present (fig. 1). The larger cells had ample cytoplasm and distinct vesicular nuclei, which harbored prominent nucleoli. When stained for Nissl substance with cresyl violet, the cytoplasm of these cells was filled with coarsely granular, deeply staining material (fig. 2). When stained by Bielschowsky's method, fine argentophil fibrils could be seen in and about these cells, which had all of the characteristics of mature ganglion cells. Whereas some of the cells were of normal appearance, many of them showed various stages of degeneration from tigrolysis and acute swelling to complete disintegration of the cell body. Occasionally binucleated ganglion cells were seen. As previously mentioned, these ganglion cells were embedded in a stroma of elongated spindle-shaped cells with deeply staining, chromatin-rich nuclei and a small amount of pale-staining cytoplasm. In intimate relationship to these cells were thin elongated fibrils, some of which stained red with Van Gieson's stain and pinkish-red with Mallory's phosphotungstic acid-hematoxylin stain. When stained by the method of Perdrau,[4a] the entire mucosa was seen to be composed of a rich feltwork of interlacing reticulin fibrils. In appearance these elongated cells closely resembled Schwann cells.

COMMENT

From the histologic description it is evident that the tumor consisted of large numbers of ganglion cells embedded in a stroma of Schwann cells. The majority of the ganglion cells were normal, with large vesicular nuclei containing prominent nucleoli, and their cytoplasm was rich in tigroid substance. Some of the ganglion cells showed regressive changes in the form of tigrolysis, acute swelling and disintegration of the cell body. As in ganglioneuroma of the spinal cord examples of which have been reported by Foerster [5] and by one of us (B.W.L.),[6] binucleated ganglion cells were occasionally seen. Their presence in the autonomic nervous system is not as significant, however, as their occurrence in the central nervous system, as they are occasionally found normally in the former. As in the case of Poate and Inglis,[1] our tumor spread diffusely throughout the mucosa and separated but did not invade the mucous glands. Our case differed from theirs, however, in that the neoplasm did not extend into the muscularis. In the case which they reported, the ileum, cecum and part of the ascending colon were involved in the neoplastic process. Since the appendix in the case which they described was grossly normal, it was not examined microscopically. The changes described in the ileum were quite similar to those found in the appendix in our case.

In order to understand better the origin of such ganglionic neoplasms in the intestine we shall review the development of the enteric plexuses.

The sympathetic plexuses in the wall of the digestive tube are derived from cells which migrate peripherally from the hindbrain and from the vagus ganglions along the course of the vagi (Kuntz [7]). As these cells become more numerous they aggregate in minute cell masses, the primor-

4a. Perdrau, J. R.: J. Path. & Bact. **24**:117, 1921.

5. Foerster, A.: Virchows Arch. f. path. Anat. **253**:116, 1924.

6. Lichtenstein, B. W., and Zeitlin, H.: Arch. Neurol. & Psychiat. **37**:1356, 1937.

7. Kuntz, A.: J. Comp. Neurol. **20**:211, 1910.

dia of the myenteric and submucous plexuses. According to Schaper,[8] some of these cells which arise by mitotic division of the germinal cells in the ependymal layer of the primitive neural tube are indifferent in character. He pointed out that in higher vertebrates many of the indifferent cells retain the capacity for further propagation by mitotic division and give rise to daughter cells of the same indifferent type, which may become differentiated into neurons and supporting cells. Thus the ganglioneuroma usually contains another cellular element in addition to the ganglionic one. Whereas the ganglioneuromas described in the brain (Courville[9]) and in the spinal cord (Lichtenstein and Zeitlin[6]) contained ganglion and glia cells and have been termed by some, therefore, ganglioglioneuroma, the homologous tumor in the peripheral nervous system usually consists of an admixture of ganglion cells and Schwann sheath cells, and for them the term "ganglioneurinoma" has been proposed.

It is well known that the ganglion cells in the peripheral ganglions are as a rule surrounded by capsules consisting of small cells homologous to the Schwann cells. The cells of the enteric plexuses, however, have been shown by Kuntz,[10] Hill[11] and others to be free from pericellular capsules, though there are scattered among them numerous small stellate cells, which some have termed the interstitial cells of Cajal and which are believed to be homologous to the glia cells (Maximow[12]).

The neuroma in our case was located in the mucosa proper, but its origin, we believe, was similar to the origin of the submucous and the myenteric plexuses. In sections treated with the hemalum-eosin stain the similarity between the ganglioneuroma of the spinal cord and that of the appendix was very striking, though in the former the supporting cells were shown to be gliocytes, and in the latter, Schwann cells. The close genetic relationship between these two types of cells, which histologically are different, is becoming more and more apparent by reason of the increasing number of cases reported in which glioma of the optic chiasm has been found in association with Recklinghausen's disease.

The malignant immature forms of neuroma occur almost exclusively in children, and the ganglioneuroma likewise appears early in life but because of its benign character may be asymptomatic for a long time.

Ganglioneuroma in other regions of the body has been reviewed by Dunn,[13] Wahl[14] and others.

SUMMARY

A case of ganglioneuroma in the vermiform appendix in an 8 year old colored girl is reported. The tumor consisted of ganglion and Schwann cells and was confined to the mucosal layer. Like ganglioneuroma in other parts of the body, this tumor is believed to have arisen from the differentiation of misplaced multipotential embryonal neurocytes.

8. Schaper, A.: Arch. f. Entwcklngsmechn. d. Organ. **5**:81, 1897.
9. Courville, C. B.: Arch. Neurol. & Psychiat. **24**:439, 1930.
10. Kuntz, A.: Anat. Rec. **24**:193, 1922.
11. Hill, C. J.: Phil. Tr. Roy. Soc., London, s.B **215**:355, 1927.
12. Maximow, A.: A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1931, p. 287.
13. Dunn, J. S.: J. Path. & Bact. **19**:456, 1914-1915.
14. Wahl, H. R.: J. M. Research **30**:205, 1914.

CARCINOMA OF MECKEL'S DIVERTICULUM

Report of a Case

JOHN M. WEIR, CHICAGO

In a summary of instances of tumor of Meckel's diverticulum reported before 1932, Michael and Bell [1] found four cases of spindle cell sarcoma, three of malignant leiomyosarcoma and two of argentaffin carcinoid tumor. Brown [2] reported a case of medullary carcinoma, Franke [3] one of adenocarcinoma, and Nygaard and Walters [4] one of fibrosarcoma. Hertzog and Carlson [5] and Price [6] reported three cases of carcinoid tumor of Meckel's diverticulum. Gray and Kernohan [7] recently reported a case of adenocarcinoma arising in heterotopic gastric mucosa in Meckel's diverticulum.

In all, there have been five cases of carcinoma, five of fibrosarcoma, five of leiomyosarcoma and five of carcinoid tumor of Meckel's diverticulum reported up to the present time.

REPORT OF CASE

A 70 year old white man, a retired railroad conductor, was admitted to the Illinois Central Hospital, Chicago, to the service of Dr. Leroy Sloan, Aug. 15, 1936. For one week prior to this he had become nauseated on attempting to eat. Associated with the onset of nausea, there had been general abdominal pain, most severe at night, and gradual swelling of the abdomen. There was no history of loss of weight. The past history was negative except for gonorrhea some years before. The patient was obese and did not appear acutely ill. The positive findings were ascites, tenderness in the left side of the abdomen and an umbilical hernia. An Ewald meal showed normal conditions. The urine and blood were normal. The Kahn test was negative. X-ray pictures of the stomach and colon were reported as showing no abnormality. Peritoneoscopic examination, August 17, revealed grape cluster-like masses on the peritoneal surfaces; 3,120 cc. of ascitic fluid was withdrawn, which contained tumor cells. The output of urine decreased markedly. On August 25 the urea nitrogen was 61.5 mg. per hundred cubic centimeters. On the next day the patient became comatose and died.

From the Department of Pathology, University of Chicago.

1. Michael, P., and Bell, H. G.: Surg., Gynec. & Obst. **54**:95, 1932.

2. Brown, R.: S. Clin. North America **13**:1283, 1933.

3. Franke, K.: Ztschr. f. Krebsforsch. **39**:206, 1933.

4. Nygaard, K. K., and Walters, W.: Proc. Staff Meet., Mayo Clin. **11**: 504, 1936.

5. Hertzog, A. J., and Carlson, L. A.: Arch. Path. **20**:587, 1935.

6. Price, I.: Brit. J. Surg. **23**:30, 1935.

7. Gray, H. K., and Kernohan, J. M.: J. A. M. A. **108**:1480, 1937.

Necropsy.—The body was that of an obese white man, estimated to weigh 200 pounds. The abdomen was dome shaped and tense. The peritoneal surfaces were extensively studded with tumor nodules. The greater omentum was massively infiltrated with the tumor, so that it measured from 5 to 6 cm. in thickness. The loops of intestine were infiltrated with the tumor and were adherent one to the other. In the right lower quadrant was a diverticulum of the ileum, firmly adherent to the posterior wall of the peritoneal cavity. The mesenteric nodes were infiltrated with the tumor. The margin of the liver was pushed above the costal border by the tumor-filled omentum, and there were nodules in the capsule. There was a small umbilical hernia. The diaphragm was at the level of the fourth rib on both sides. There were no significant changes in the viscera of the pleural and pericardial cavities. The liver weighed 1,450 Gm. and was extensively studded with tumor nodules. The gallbladder and bile ducts were normal. The spleen was normal, as was the pancreas. At the head of the pancreas was a yellow calculus, 1 cm. in diameter, lying in the peritoneal fat. The stomach, duodenum and jejunum were normal except for an infiltration of tumor cells into the serosa of the jejunum. In the lower third of the ileum was a diverticulum 10 cm. in length. At the tip of the diverticulum was a firm mass of tumor tissue. When the diverticulum was opened, the tumor appeared to arise from an elevated mass with a depressed center in the mucosa. The mass in the diverticulum measured 3 cm. in diameter. Below the level of the diverticulum in the ileum were two areas in which the tumor, infiltrating the serosa, had eroded through the wall of the bowel to produce an ulceration of the mucosa. The tumor in these lesions clearly arose in the serosa, and the mucosa surrounding the ulcer was normal. The colon and rectum were normal. The left adrenal was normal. The right adrenal was composed of cystic cavities measuring from 2 mm. in diameter at the lower pole to 3 cm. in diameter in one large cyst at the upper pole. In the wall of the largest cyst was a yellow nodule 1 cm. in diameter and 5 mm. in thickness. The walls of the cysts were fibrous. There was no tumor tissue in the immediate vicinity of either adrenal. The lower pole of the right adrenal was adherent to the right kidney. The kidneys were normal except for a cyst, 2 cm. in diameter, at the upper pole of the right kidney. The genito-urinary tract was not abnormal for the age.

Histologic Observations.—The diverticulum presented a large ulcerating growth of typical adenocarcinoma with marked acute inflammatory reaction in its vicinity. The cells were highly anaplastic, often with large hyperchromatic nuclei, and generally occurred in cords, with abortive attempts at forming glands. Some were of signet ring character and were apparently secreting mucus. They invaded the lymphatics and blood vessels and spread over the serous coat, where they produced young granulation tissue. There were large areas of necrosis and relatively little fibroplastic reaction, although eosinophils were numerous. The adjacent mucosa resembled that of the ileum and showed no evidence of gastric mucosa. The ileum presented large tumor masses in the serosa, which in places ulcerated through the mucosa. These tumors clearly invaded the ileum from the serosa, and the surrounding mucosa was normal. The right adrenal presented some portions that seemed to be normal. There were also areas that consisted of cystic cavities apparently containing coagulated protein. In places, this for-

mation invaded and destroyed the adrenal tissue. There were nodules of fibrous tissue that seemed to represent organization of some of the cystic spaces. There were also large areas of dense hyalinized scar tissue, with some calcific deposits, accumulations of cholesterol slits and some blood pigment. Apparently the adrenal had been partly destroyed and greatly disarranged by the formation of collections of cystic cavities, into which hemorrhages had occurred. The appearance indicated a lymphangiomatous formation arising within the adrenal.

SUMMARY

Carcinoma of Meckel's diverticulum is rare. Only five cases have been found recorded in the literature, to which is added a sixth.

General Review

SHOCK, ITS MECHANISM AND PATHOLOGY

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(Concluded from page 663)

A CRITIQUE OF METHODS

Attacks on this problem have been extremely diversified in character. In some the experimental procedures were intricate and included technical details such as would affect the accuracy of the data and conclusions. Readers lacking practical experience with problems in this field are unable to judge critically the merits of the evidence presented. For this reason an evaluation of certain technical features is in order.

The experiments tending to show that local loss of blood and fluid provides a satisfactory explanation for shock deserve analysis. Blalock's results indicated, if one disregards the factor of error mentioned in a preceding section, that local loss of blood and fluid averaging 35 per cent of the total blood volume occurred in the traumatized areas. This was assumed to be sufficient to cause death as by hemorrhage. However, Milroy showed that animals are able spontaneously to restore the blood to its original volume in a few hours following a loss of more than one third of the total blood volume. Roome, Keith and Phemister showed that the amount of blood necessary to be withdrawn to produce death in anesthetized dogs if withdrawn within an hour was 58.6 per cent of the total blood volume. If the blood was withdrawn more slowly, the amount necessary was 70 per cent of the total blood volume. It is recalled that loss of blood by hemorrhage in man brings the subject to a critical state only when the hemoglobin and red cells have been reduced to about 25 per cent of their normal values. Losses of blood comparable to these were rarely reported as resulting from experimental trauma.

All observers agree that a reduced total blood volume is an outstanding feature of shock. Any loss of blood and/or fluid locally will contribute to that feature, and its importance will be in proportion to the amount of blood and/or fluid lost. In some of the experiments the amounts of extravasated blood found in the tissues, the visible ischemia of the viscera as seen post mortem and the evidence of hemodilution shown by examination of the blood—all indicated that hemorrhage was the predominating factor.

Toxic Substance in the Blood.—Efforts have been made, by transfusions of blood and otherwise, to demonstrate poisonous substances in the blood of animals in shock. The almost uniformly negative results of such experiments have been emphasized by some as invalidating the conception of traumatic toxemia. Physiologists have raised this objection less frequently than surgeons, perhaps because they remember that protein and other colloidal substances are not absorbed from tissue spaces into the blood stream but via the lymphatics. Similar experiments made on blood drawn from the vena cava proximal to the mouth of the thoracic duct, or on blood obtained from the pulmonary arteries, have not been reported. But negative results from blood so obtained would have little weight. Shock developing from extensive tissue injury, as burns or trauma, is a gradual affair extending over many hours. It is not necessary to assume that, even in cases in which the condition is of the utmost severity, an effective quantity of toxic substance will be contained in the entire volume of an animal's blood at any one time. If knowledge of the mechanism by which a snake bite produces death had depended on demonstrating an effective amount of venom in the bitten animal's blood, understanding of that mechanism might as yet be largely conjectural.

Contributory Effects of Anesthesia.—Moon and his collaborators early in their experiments on shock gave sodium phenobarbital intravenously to a dog, 0.3 Gm. per kilogram of body weight. Shortly afterward the blood pressure fell 93 mm. of mercury although no experiments had begun. They immediately abandoned barbital as an anesthetic and acquired a distrust for data derived from experiments in which this anesthetic was used. Robinson and Parsons made studies on shock under sodium phenobarbital anesthesia. They recorded the observation that in some of the dogs "spontaneous shock" developed. Blalock found that in an occasional dog a fall in blood pressure occurred which was due to "an abnormal sensitivity to barbital." "In several animals there was a rapid decline in the blood pressure shortly after giving the barbital. These experiments were discarded. The level of the mean blood pressure was used as a criterion of the degree of shock" (Blalock, reference b, p. 962; reference d, p. 599). One infers that if experimentation had begun before barbital caused the pressure to fall, the results of the experiments were considered dependable. It was recorded that in one instance a dog under barbital anesthesia succumbed to a loss of blood amounting to only 1.5 per cent of body weight. In two other instances in the same series death occurred from the effects of barbital without any loss of blood. Yet such abnormal susceptibility to hemorrhage under barbital anesthesia was not regarded as a possible factor of error in any of the conclusions.

Frequently, in a wounded soldier whose condition was not critical, severe shock developed immediately on anesthetization for operation. This was reported as a common experience in the medical military service during the war. Dale and his associates produced fatal shock in etherized cats by injections of 1 or 2 mg. of histamine. But unanesthetized cats frequently will withstand ten times that dosage. Complete anesthesia, while usually insufficient to produce failure of the circulation of itself, comes dangerously near the threshold level in many instances. The barbiturates in the dosage used in animals approach the danger point very closely. The experience of Moon and his associates with anesthetics leads them to endorse Mann's opinion that in many instances the recorded phenomena resulted from the deep prolonged anesthesia and not from shock. He believed that this accounts for much of the contradictory experimental evidence reported.

The similarity between hemorrhage and shock in their clinical manifestations has caused confusion. Suppose one wishes to compare or differentiate the pharmacologic properties of two drugs that are similar in their action. One would not give both drugs simultaneously to the same animal and attempt to draw conclusions from the results. Certainly in such an experiment one would not employ an anesthetic the effects of which resemble even remotely the action of the drugs in question. It is equally illogical to produce, under deep narcosis, trauma sufficient to cause death by shock and accompanied by hemorrhage or loss of fluid sufficient to cause serious disturbance of the circulation. Results from experiments so arranged cannot be useful in distinguishing the mechanism of shock from the effects of hemorrhage. Those results may be due to the anesthetic, to the trauma, to the associated hemorrhage or in part to each.

Critical analysis of the methods in common use for the production of shock reveals several objectionable features:

A decline in blood pressure is not an accurate criterion. It often results from other conditions, and it does not occur early in shock but appears only after blood volume and volume flow have been reduced.

The deep narcosis used often causes a fall in blood pressure and other shocklike manifestations.

Large amounts of blood and fluid are lost incident to the trauma. In some reports it was evident that the workers were dealing almost entirely with hemorrhage.

It is not possible to study minor degrees of shock or to make later observations, since it is impossible to keep the animal in a condition suitable for study on subsequent days.

Under such conditions of experimentation the recorded phenomena may have been due to the narcotic, to the trauma, to the associated

hemorrhage or in part to each. This combination of indeterminate factors has led to undependable conclusions and to confusion.

SEARCH FOR ADDITIONAL EVIDENCE

Reports tending to show that shock may be explained as due to local loss of blood and fluid were widely accepted and caused many to abandon the explanation that substances absorbed from injured tissue may cause deficiency in the circulation by producing capillary atony. Instances in which the evidence inadequately supported the conclusions were not apparent to casual readers, and many lost their bearings in a maze of contradictory results and interpretations. In such a dilemma the need for additional evidence was imperative.

A survey of medical literature revealed the remarkable fact that in no instance had shock been investigated by the methods used by pathologists. Shock was regarded as a physiologic disturbance unaccompanied by characteristic morbid anatomic features. The belief that examination of tissues and organs would show nothing of significance had been accepted without question.

Had the methods of pathology been combined with those of physiology, much confusion might have been avoided. This was done in the case of histamine. The interpretation that histamine produces atony of the capillaries, resulting in permeability, leakage of plasma, loss of blood volume, hemoconcentration and circulatory failure was tested by Rich. He produced both local and general effects with histamine in cats, and made gross and microscopic observations on the circulatory changes seen in the viscera during life and post mortem. These circulatory changes confirmed Dale's interpretations. Rich concluded that the failure of the circulation which characterizes histamine shock results from dilatation of the peripheral vascular stream bed.

Occasional mention had been made of similar changes in the circulation following death associated with failure of the circulation like that of shock. Cumin (1823) described edema, effusions and an appearance of deep congestion of the viscera, serosae and mucosae following death from burns. Such changes are accepted as the characteristic appearances following death from burns (Bardeen; Pack). Sherrington and Copeman noted concentration of the blood and development of tissue edema as the circulation became inefficient during operations within the abdomen.

Turck noted the purplish color and venous congestion of the abdominal viscera following injection of tissue extracts and of fluid from the gastro-intestinal tract into dogs. Romberg and Pässler mentioned such changes following death by failure of the circulation incident to severe infections and intoxications. They recorded marked congestion of the

tiniest vessels, minute hemorrhages in the endocardium, in serous surfaces and in the gastro-intestinal mucosa, and marked congestion and edema of the lungs and edema of the intestinal mucosa as postmortem features in such cases. Coca described pulmonary congestion and capillary hemorrhages following injection of foreign serums. Such circulatory changes in the thoracic and abdominal viscera have been recorded many times in experiments on anaphylaxis.

Whipple, Stone and Bernheim produced shock in dogs by intravenous injection of fluid obtained from a closed loop of bowel. This was followed by vomiting of fluid containing blood and bile, liquid bloody defecation, salivation and collapse. The pulse became rapid and weak, and the temperature and blood pressure declined. There was congestion of the lungs, liver, kidneys and gastro-intestinal tract. The small mesenteric vessels were distended and conspicuous. The mucosa of the small bowel was swollen and had a deep purple velvety appearance. The engorged villi were seen as tiny red specks in the mucosa. Microscopically there was enormous engorgement of the vessels in the villi, and the kidney, spleen and liver showed great congestion.

Bayliss observed visible dilatation of the minute blood vessels of the intestines following injection of watery extract of muscle in cats and following shock produced by trauma. Keith noted marked congestion and edema in two cases of shock from wounds received in battle. Other tissues were described as abnormally moist.

Erlanger, Gasser and their associates produced shock by retarding the venous or the arterial circulation by manipulation of the viscera and by massive injections of epinephrine. A marked decrease in plasma volume, a loss of total blood volume ranging from 30 to 50 per cent, and an increase in concentration of the blood occurred following each method. They regarded the decrease in blood volume as the essential feature in the mechanism of shock. This decrease resulted from several factors: transudation of plasma, dilatation of capillaries and small veins, with jamming of corpuscles in them, great slowing of the circulation, development of absolute stasis in some parts of the vascular system and small extravasations of blood into the tissues, particularly the mucosae. They noted engorgement of the minute vessels and transudation of plasma before the blood pressure began to decline. Dilatation and stasis in capillaries and venules lower the effective blood volume, while capillary hemorrhages and transudation of plasma lower the actual blood volume.

The findings were similar following all types of shock in over one hundred animals. The most constant feature was congestion of the intestinal mucosa, especially that of the duodenum and ileum. The lining of the bowel had the appearance of deep red velvet and contained

punctate hemorrhages. There was blood in the intestinal lumen in 60 per cent of the cases. The large abdominal veins were collapsed, but the minute veins and capillaries were distended with closely packed corpuscles, proving their involvement beyond peradventure. Congestion of the vessels of the intestinal villi accounted for the purple velvety appearance seen grossly. "The most remarkable feature though is brought to light by microscopic examination of the intestines: in all types of shock the capillaries and venules of the villi are tremendously distended by solid masses of red corpuscles" (Erlanger, Gesell and Gasser). They believed that sequestration of blood in the minute vessels and transudation of plasma into the tissues were responsible for the decrease in blood volume and the increase in concentration of the blood.

Mason and his co-workers found marked hyperemia of the abdominal viscera and capillary hemorrhages following shock produced by injection of liver substance into the peritoneal cavities of dogs. Blalock described similar appearances in dogs following injection of fluid from traumatized limbs. Other similar incidental observations are found in articles on this type of failure of the circulation, but only a few authors suggested that there was an etiologic relationship between these pathologic features and the mechanism of the circulatory deficiency.

A REVISION OF EXPERIMENTAL TECHNIC

Moon and his associates believed that examinations of the viscera following shock might produce evidence either confirming the observations just cited or supporting the interpretation that shock results solely from local loss of blood and/or fluid. Methods were devised to eliminate the objectionable features set forth under "A Critique of Method." It had been shown that shock is accompanied regularly by hemoconcentration. Experimental trials on animals and observations on man showed that hemoconcentration develops before changes in pressure occur. Accordingly, hemoconcentration was adopted as a criterion rather than changes in pressure. Shock was induced without hemorrhage or trauma by introducing muscle substance intraperitoneally, by injecting extracts of tissues, by injecting bile and by other procedures. These methods eliminated deep narcosis and hemorrhage as factors. They furnished another advantage of great importance: Shock of varying degrees can be produced, and observations can be made on its later stages and sequelae, uncomplicated by other factors.

One method used was as follows: A quantity of muscle was excised aseptically from a freshly killed normal dog. This was ground finely in a meat chopper and suspended in physiologic solution of sodium chloride under aseptic precautions. Varying quantities of this preparation were introduced into the peritoneal cavities of normal dogs under light ether

anesthesia. Records were made of the pulse rate, respirations, temperature, hemoglobin content and red cell count three times each day before and after this procedure.

When large doses, 5 Gm. or more per kilogram of body weight, were used, severe illness developed within two or three hours. Thirst was evident, but vomiting followed when fluids were taken. The vomitus contained bile, mucus and flecks of blood. The urine was scanty and often contained blood. Diarrhea frequently developed, and the feces showed mucus and bloody fluid. The pulse rate and temperature rose, and, although the peripheral parts became cold, the rectal temperature remained high until death. The circulation became retarded, and it was difficult to secure blood by venipuncture because of the flaccid condition of the veins. Also it sometimes was difficult to obtain capillary blood from ear, nose or paw for examination. Hemoconcentration was a regular feature. It sometimes developed within an hour after the implantation of muscle. It occurred before the arterial blood pressure began to decline and was progressive. The degree of concentration was proportionate to the apparent illness of the animal. A condition of collapse, relaxation and stupor preceded death.

Smaller doses of muscle substance produced the same signs of illness, but less rapid in development and in degree. Death did not occur so early. Recovery often occurred following the use of doses of 3 Gm. or less per kilogram of body weight.

Exactly similar manifestations followed the intraperitoneal or intravenous injection of watery extracts of dog muscle and of other tissues, of bile or its salts, of bacterial toxins and cultures, of histamine, snake venom and of other substances.

Moon and his associates produced shock also by trauma to the muscles, by intestinal manipulation and by burns. In these cases ether anesthesia was used, but only during the operation. Subsequent pain was prevented by small doses of morphine. The signs of illness, including progressive hemoconcentration, and the manner of death in these cases were the same as described. The conditions provided by many of the agents used approximated closely those under which shock develops in man.

PATHOLOGY OF SHOCK

Moon and his associates reported their observations on the viscera as follows:

> The superficial veins are collapsed and bloodless. The blood in the heart and large vessels and in the parenchyma of organs is dark and thick and has failed to clot. Frequently it has a deep purplish cast. The serous surfaces are diffusely congested and appear cyanotic. In severe cases they contain ecchymoses, and the cavities contain blood-tinged fluid. The bowels are atonic, relaxed and distended. The vessels along the mesenteric attachment are engorged and prominent. The

mucosae are congested and edematous and frequently contain ecchymoses. Their appearance resembles purple velvet. Occasionally there is bloody fluid within the lumen of the bowel. The fluid in the stomach may contain visible blood or brown flocculi. These contain hemoglobin, and the fluid contains serum albumin. The lungs are intensely congested either diffusely or in areas, producing a mottled appearance. Microscopically, the capillaries are distended and the venules are dilated and packed with corpuscles. Hemorrhages from the capillaries are numerous. Marked edema is present, particularly if death has been delayed somewhat. The edema fluid has a high protein content, and its specific gravity approximates that of the blood plasma. The liver and kidneys are deeply congested. Blood oozes and drips from the parenchyma when this is sectioned. The cells regularly show parenchymatous degeneration. Patches of hemorrhage from capillaries occur in the medulla, and numerous red cells are observed within the tubules in such areas.

The spleen usually contains less blood than it does normally. In dogs it is firm, contracted and dry. The heart has a purplish, cyanotic color, and there is engorgement of the venules and capillaries in the myocardium. If death has been delayed somewhat the myocardial fibers show evidence of degeneration. The adrenal glands participate in the capillary congestion seen elsewhere but they show no other changes. The meninges are congested and edematous, and occasional punctate hemorrhages are found in the brain (reference d, p. 326).

In several experiments (Moon and Morgan, reference i, p. 782) when hemoconcentration indicated that shock was developing, an intravenous injection of a neutral solution of trypan blue was made. Such colloidal dyes are retained in the blood under normal conditions, but they pass out rapidly into the tissues if the permeability of the capillary walls is increased. After death there was marked bluing of the mucous and serous surfaces and of the kidneys, bladder and other tissues. The edema fluid present in the serous cavities was distinctly blue. These results indicated abnormal permeability of the capillaries in systemic areas. The permeability was not limited to the areas adjacent to the injury.

The authors reported that circulatory changes of this kind followed shock produced by each agent mentioned. The changes were interpreted as indicating loss of tonus affecting the capillaries and venules systemically, resulting in stasis and in an increased volume capacity of the vascular system. The edema, serous effusions and capillary extravasations were regarded as evidence of increased capillary permeability. They believed that these factors account for the decrease in blood volume and for the hemoconcentration which are characteristic of shock.

Moon (references b, c and g) reported similar congestive, edematous and hemorrhagic conditions of the viscera following shock in man. His observations were corroborated by reports of necropsies following shock taken from the official records of the United States Army Medical Service. Moon found that shock occurred frequently in conditions other

than trauma or extensive surgical procedures. These conditions included extensive burns, poisoning with various substances, metabolic intoxications, abdominal emergencies and infections of unusual severity. Failure of the circulation with hemoconcentration occurred in these illnesses, and the postmortem observations were of the same character as described. These findings substantiated the previous observations of others who had described the development of shock in various conditions of disease (Romberg and Pässler; Atchley; Warfield; Eppinger and his associates).

Moon emphasized that shock may be differentiated from hemorrhage by the following features: Subsequent to hemorrhage the blood shows dilution, the viscera are pale and ischemic, and the tissues are dry. During the development of shock the blood is concentrated, and post mortem the viscera are congested, the minute vessels engorged and the tissues edematous.

A type of pulmonary edema which occurs frequently in man was reproduced experimentally (Moon and Morgan, reference j) by simple procedures. Sublethal degrees of shock induced by various means resulted in circulatory failure accompanied by hemoconcentration and pulmonary edema. They showed that this resulted from leakage of plasma through capillary walls and that its mechanism of origin was integral with that of shock. They forecast that such edema may be produced by any agents capable of causing injury to capillary endothelium, provided they are given in a dosage sufficient to affect the circulation but not sufficient to cause immediate death.

Many animals in which shock of a sublethal degree was produced died of pneumonia, preceded by pulmonary edema. Moon (references a, c and j) believes this mechanism accounts for many cases of terminal pneumonia in man. Pneumonia, preceded by congestion and edema of the lungs, develops following severe trauma, prolonged surgical operations, burns, metabolic intoxications, intestinal obstructions and severe infections. Lungs in which the circulation is sluggish and in which spaces are filled with edema fluid, as in shock of sublethal degree, present a stage already set for the development of terminal pneumonia.

ESSENTIAL FEATURES AND A DEFINITION

I have found no disagreement, in recent discussions of shock, concerning the regular occurrence of certain features. There is agreement that the heart is not primarily at fault and that the disturbance does not originate in the nervous mechanism controlling it or in the vasomotor system. A marked decrease in the total blood volume and an increase in concentration of the blood have been recorded by all who have obtained data on these points.

Likewise the volume output of the heart per minute or, as is often stated, the volume flow of arterial blood is markedly decreased. This feature is technically more difficult to demonstrate, and hence not so many workers have emphasized it. Henderson noted a decrease in the volume flow regularly before the arterial pressure declined. Erlanger and his associates confirmed this point. Gesell showed that the volume flow may decrease to 25 per cent of the normal without change in the arterial pressure. Wiggers concluded that a reduced volume output is the predominant factor in shock. Freeman recently substantiated these observations and demonstrated conclusively that in shock blood pressure is maintained at the expense of volume flow by arterial vasoconstriction. This corroborates many previous observations that in shock the arteries are in a state of maximal contraction. Freeman's results indicate that so long as arterial constriction can compensate the developing disparity between the volume of blood and the volume capacity of the vascular system the blood pressure does not decline notably. A sustained decline indicates that the disparity mentioned is no longer compensated.

It appears that the physiologic features mentioned are essential in the mechanism of shock and that they may be used to differentiate it from other conditions having similar clinical manifestations. I have proposed this definition: *Shock is a deficiency in the circulation, not cardiac and not vasomotor in origin, characterized by decreased total blood volume, decreased volume flow and by hemoconcentration.* The latter feature appears early, is easily detected and hence is useful as a criterion of shock, whether this occurs clinically or is produced experimentally.

Other features regularly associated are: anoxemia of a high degree, a decrease in the alkali reserve (except in shock following intestinal obstruction) and in basal metabolism, an increase in the lactic acid, glycogen and nonprotein nitrogen of the blood and a decrease in the chlorides. In advanced stages of shock the coagulability of the blood is markedly decreased. Often it will remain unclotted in a glass tube for hours. Failure of the blood to clot is usually noticed at necropsy.

Other features are variable: Immediately following injury there is leukopenia, but later the number of leukocytes may range from 30,000 to 60,000. This occurs within a few hours and is not due to infection (Cannon, reference c). Dale and his co-workers reported leukopenia in fatal histamine shock in cats. Smaller injections of histamine are followed by leukocytosis (Moon, Lieber and Kennedy). Burns sufficient to produce shock cause immediate high leukocytosis like that following extensive trauma (Locke; Bardeen, and others).

Variations in temperature are likewise inconstant. In shock following wounds incurred in battle or following surgical procedures or poisoning, as with mercury bichloride, the temperature declines. Shock inci-

dent to burns, heat stroke, intoxications or severe infections is often accompanied by high temperatures. Following wounds incurred in battle the respirations are rapid and shallow, with an occasional deep sigh (Cannon, reference c). Usually the respirations during experimental shock in dogs are slow and deep.

Vomiting is a prominent feature in dogs and in man. The vomitus may contain visible blood or "coffee grounds flocculi," which contain hemoglobin, and it is usually tinged with bile. Diarrhea also is frequent but not regularly present. The feces often contain mucus and blood.

Anoxemia is a most important feature and is explainable as incident to the decreased volume flow. Janeway and Jackson, also Erlanger and others, produced shock by reducing the volume flow mechanically. A clamp on the vena cava or on the abdominal aorta was adjusted until the arterial pressure was brought below 50 mm. After two or three hours this partial obstruction to the circulation was removed. Shock developed shortly after the reestablishment of the circulation. Mann (reference d) accomplished the same result by ligating for a time the veins and lymph vessels leading from the limbs. Shock of varying degrees developed, and death followed if the stasis was continued long. "The results following the release of the ligatures are due to damage to the tissues in the involved area and the passage of toxic products from the injured tissues into the general circulation." Apparently the damage in such experiments resulted from stasis of circulation and deprivation of oxygen. Cannon and Cattell reduced the volume flow of blood by a mechanical device which controlled and limited filling of the heart. When low arterial pressure was thus maintained for a time the low pressure persisted without artifice.

Prolonged arterial constriction as produced by epinephrine may cause shock by the same mechanism as mechanical interference with the circulation. Certain investigators (Crile, Bainbridge and Trevan; Gasser, Meek and Erlanger; Lamson; Freeman, and others) have shown that repeated injections of epinephrine are followed by failure of the circulation with hemoconcentration and other features of shock. This phenomenon was interpreted (Freeman; Cannon, reference d) as due to tissue anoxia produced by maximal arterial constriction. They advanced this as evidence supporting the possibility that shock may arise from hyperactivity of the sympatho-adrenal system.

In each of the instances cited the development of anoxia in extensive areas of tissue led to the development of shock. The relationship of this to shock otherwise produced will be discussed later.

Water Balance.—Complete removal of the adrenals produces, after an interval of several days, all the physiologic disturbances which are characteristic of shock. Injections of an extract of adrenal cortex will restore such animals to a normal physiologic state. Injections of medul-

lary extract—epinephrine—have no such effect. Recently there has been a tendency to interpret shock as due to a disturbance of water balance perhaps arising from deficiency of adrenal cortical function. The conditions which govern the movement of water between the blood plasma and the cytoplasm of the tissues are not entirely understood. Osmotic pressure, capillary blood pressure, ionic and molecular concentration and perhaps other physicochemic forces, as well as hormonal influences, are factors influencing the distribution of water (Drinker and Field; Landis).

Let it be emphasized that the action of these forces in maintaining a physiologic ratio between the composition of intravascular and that of extravascular fluid is conditioned on the presence of a normal semipermeable endothelium between them. Capillary walls so altered in physiologic condition as to permit whole plasma and even erythrocytes to pass freely into the tissue spaces are incapable of maintaining any effective differential between intravascular and extravascular fluids.

In dogs whose adrenals have been entirely removed shock develops gradually after an interval of from five to seven days. If shock-producing agents exerted their effects by partial or even total inhibition of adrenal function, these effects should not be shown for several days. Shock develops within a few hours following injury. This fact makes untenable the hypothesis that deficient function of the adrenal cortex is an essential factor in the mechanism of shock. It is fallacious to reason that, because lack of cortical hormone produces shock, all shock is due to lack of cortical hormone.

A VICIOUS CIRCLE

Many have commented on the fact that the deficiency of circulation characteristic of shock tends to become irreversible. If the blood pressure remains below from 70 to 80 mm. for several hours, the condition acquires a self-perpetuating quality and progresses. A stage is reached at which neither the body's physiologic reactions nor any known therapeutic measures are effective.

Cannon (reference c, p. 162) noted the operation of this vicious circle in seriously wounded soldiers. He attributed it to several factors: Deficient circulation lowers the metabolism. With lowered oxidation the production of heat is diminished. Low temperature contributes to capillary atony and increases the viscosity of the blood. There is progressive loss of fluid by perspiration and vomiting. Fluid given by mouth or by injection is not absorbed or retained. Transudation of plasma causes concentration of the blood and increases its viscosity. Thick viscid blood has an increased coefficient of friction, which tends

to impede circulation. As more blood stagnates in capillary areas the volume returned is diminished and the volume flow of arterial blood is reduced. He suggested several other contributory factors.

Anoxia is a highly important factor in the self-perpetuating cycle of shock. Krogh (p. 335) stated that temporary lack of oxygen causes prompt increase in capillary permeability, followed by irreversible stasis. Restoration of arterial circulation after fifteen minutes' occlusion does not restore capillary circulation in such areas. Once the lack of oxygen in a large area of tissue is sufficient to produce capillary atony, the condition tends to become self-perpetuating. Plasma escapes into the tissues, and the minute vessels become jammed with corpuscles. This impedes the circulation, decreases the blood volume and the volume flow, and increases the anoxia. As this cycle progresses the reestablishment of circulatory efficiency becomes progressively more difficult. The vicious circle is shown diagramatically in the accompanying figure.

INTEGRATION OF EVIDENCE

The facts which have resulted from observations on large numbers of casualties in battle, from numerous and diversified experimental attacks on the problems, from increased knowledge of capillary structure and function and from observations on the visceral changes which accompany shock may all be assembled, like pieces of a jigsaw puzzle, into an intelligible picture. The accompanying diagram is an attempt to present that picture visually.

Diverse agents [2] and conditions affect the minute vessels by producing *capillary atony,* which results in the pathologic changes characteristic of shock. One of these, hemoconcentration, is a most valuable diagnostic sign. Others—dilatation, stasis and permeability—cause a decrease in both the actual and the effective *blood volume.* The *volume flow* is thereby reduced, and *deficient delivery of oxygen* causes *tissue anoxia.* Temporary lack of oxygen in the tissues causes *capillary atony.* This effect completes the cycle and explains the self-perpetuating tendency which becomes evident when the condition is severe or the time factor extended.

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2. I have included under the clinical conditions of occurrence only those with which I have had personal experience. These presented the characteristic clinical evidences of shock, and necropsy showed the pathologic features described. Also, I have included in the list of agents used experimentally only those which my associates and I have found by actual trial will produce regularly the shock syndrome in dogs, accompanied by hemoconcentration and represented post mortem by the pathologic features described. It is not believed that the conditions and agents listed represent all those which will produce shock. Many others, with which we have not had experience, may affect the circulation in the same manner. With few exceptions neither the clinical patients nor the experimental animals had been subjected to deep narcosis or to significant loss of blood.

Capillary dilatation combined with loss of plasma volume causes disparity between the volume of blood and the volume capacity of the vascular system. Maximal arterial constriction will compensate this disparity for a time. This compensation is at the expense of volume flow. The peripheral parts become relatively bloodless and vital organs suffer lack of oxygen. When this mechanism of compensation is no longer effective, the blood pressure declines progressively. At this stage the condition is usually irreversible.

Anoxia in the tissues may exert a similar action through *deficient oxidation* and *defective metabolism.* Undoubtedly other contributory factors mentioned by Cannon are important. Their action contributes to reduce blood volume, reduce volume flow or bring on other chief conditions in the vicious circle.

THE MECHANISM OF SHOCK

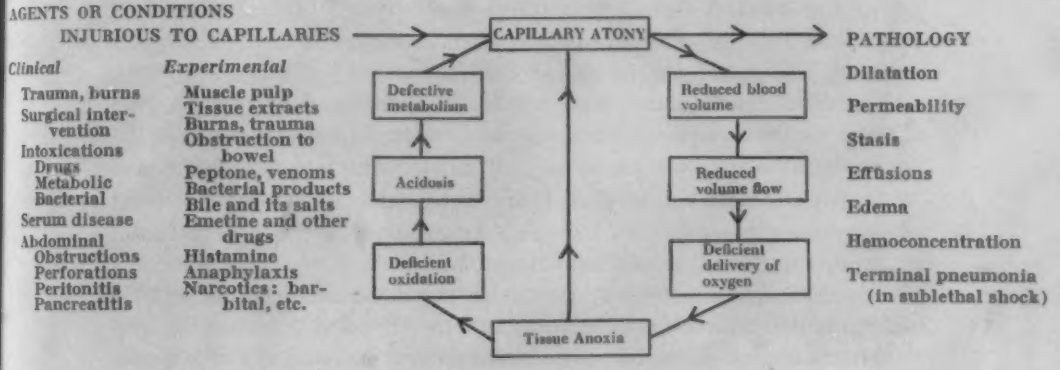

Diagram illustrating the vicious circle of shock.

The cycle may be initiated at other points than that of *capillary atony.* Loss of blood by hemorrhage may reduce the blood volume sufficiently to produce *anoxia,* which, by causing *capillary atony,* will perpetuate the deficiency in the circulation. It is well known that following a hemorrhage sufficient to lower the percentage of hemoglobin to 25 or below, immediate transfusion will be effective. But after a delay of several hours transfusion may be valueless. The condition may have progressed to an irreversible stage by the operation of the cycle. Clinicians have observed the dilution of blood which follows hemorrhage, as fluid is absorbed from tissues and other sources. This is understood as the physiologic mechanism for the restoration of blood volume. Frequently it has been noted that following such dilution the blood again tends to concentrate; i. e., the hemoglobin rises. Such a change is ominous. It may not mean that new red cells and hemoglobin have been

formed but that the endothelium in extensive areas has lost its ability to retain fluid.

Any direct loss of blood or of fluid lowers *blood volume* and contributes to deficient delivery of oxygen. Those who have confused shock with hemorrhage have been correct in the belief that the mechanism of death is identical in both conditions. The error lay in the assumption that because hemorrhage will produce shock, all shock is produced by hemorrhage.

Shock may be induced by procedures which *reduce the volume flow* of blood. This is exemplified in the results of several workers who produced temporary mechanical obstruction of the circulation and noted that shock developed following release of the obstruction. Their interpretation that this was due to anoxia and to deficient metabolism in the tissues appears to coincide with the picture.

Shock produced by excessive arterial contraction such as occurs with use of epinephrine or in hyperactivity of the sympatho-adrenal system also results from *reduction in volume flow*. I believe that those authors correctly interpreted the results as due to *anoxia*, with *capillary atony* as a consequent feature. But it may be questioned whether hyperactivity of the sympatho-adrenal system alone is an important factor in shock in most instances.

Deficient delivery of oxygen from causes other than those discussed will produce the syndrome of shock. An example of this is seen in the characteristic clinical evidences of shock when coronary occlusion occurs and death is not immediate. In this instance the deficient delivery of oxygen is due to inadequate cardiac action.

The examples discussed have illustrated *deficient delivery of oxygen*. An inadequate supply of oxygen is equally effective in initiating progressive deficiency of the circulation. This is seen in asphyxia from all causes. It is well known that oxygen must be supplied immediately to an asphyxiated subject if favorable results are to follow. Delay affords time for *tissue anoxia* to affect the capillary endothelium in extensive areas and to produce a condition not reversible by supplying oxygen.

It is probable that a self-perpetuating failure of the circulation may originate in other items shown in the diagram. However, instances of *deficient oxidation, acidosis* or *defective metabolism* arising from causes other than *anoxia* are not so easy to furnish as examples of shock originating from these factors.

The congestive, edematous and hemorrhagic changes which accompany shock are directly related to its mechanism of origin. They are commonly misinterpreted as indicating passive congestion. The term "acute venous congestion" or "capillo-venous congestion" would designate the condition more accurately. The term *congestive heart failure* as

designating the cause of death is a misnomer in many cases. In the absence of demonstrable cardiac pathologic changes the term "congestive failure of the circulation" would be more appropriate.

SUMMARY

Several proposed explanations of shock have lacked confirmation by subsequent investigation. The theory of vasomotor exhaustion is untenable since it has been shown that the vasomotor mechanism is active and its reflexes not abolished until the subject is moribund. In shock the arteries are not relaxed but are maximally contracted. It may be concluded safely that the heart, the arteries and the nerve agencies controlling their action are not primarily involved.

Acapnia is an inadequate explanation. Shock may be induced in animals while the carbon dioxide content of the blood and tissues is maintained at or above the normal level. Fat embolism should not be confused with shock. An important physiologic difference is that fat embolism is accompanied by increased venous pressure while in shock venous pressure is decreased. Shock may be produced experimentally by methods which exclude acapnia and fat embolism.

A decrease in alkali reserve usually develops in shock, but the evidence indicates that this is due to a deficiency in oxidation, resulting from a reduction in circulation. It is a result rather than a cause of the circulatory deficiency.

Inability to distinguish between the effects of narcosis, those of hemorrhage and those of the agent or injury used in the experiment has helped to make conclusions undependable and to cause confusion. The substitution of hemoconcentration for change in blood pressure as a criterion aids in avoiding this confusion.

The experiments and observations made in testing theories and in seeking explanations have established a group of essential physiologic features which may serve as a definition: *Shock is a circulatory deficiency, not cardiac and not vasomotor in origin, characterized by decreased total blood volume, decreased volume flow and by hemoconcentration.*

An imposing array of evidence has accumulated from diverse sources, supporting the interpretation that substances absorbed from injured tissues produce progressive circulatory deficiency by their effects on the minute vessels in systemic areas. Under the influence of these substances, and of other agents, the capillaries and venules become atonic and dilated and their walls abnormally permeable to the fluids of the blood. This results in stasis and leakage of fluid from the vessels. It also increases the volume capacity of the vascular system, reduces the total volume and the volume flow of blood, increases its concentration and produces edema.

This explanation is supported by investigations on capillary function and capillary reactions in living tissues. It has been corroborated further by the demonstration of corresponding gross and microscopic circulatory changes in the viscera. Shock, like other conditions of disease, is accompanied by morphologic changes etiologically related to its mechanism of origin.

The evidence does not support the idea that local loss of blood and/or fluid at the site of injury is an adequate explanation for shock. But such loss of fluid is a factor. It contributes to the circulatory deficiency in proportion to the volume of blood and fluid lost.

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Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—Gustave Roussy, professor of pathology, has been appointed rector of the University of Paris.

Howard J. Shaughnessy has resigned as chief of the division of laboratories of the Department of Public Health of Illinois to accept the associate professorship of bacteriology and public health in the University of Colorado.

Albert von Szent-Györgyi, professor of medicine in the University of Szeged, Hungary, has been awarded the Nobel Prize in physiology and medicine, 1937, for "his discoveries on the biological process of combustion, especially in relation to vitamins A and C."

Louis Gross, director of laboratories of the Mount Sinai Hospital, New York, died on Oct. 17, 1937, at the age of 42 years. A sketch of his life will be published later.

Medical Fellowships.—Fellowships in medical sciences will be awarded by the Medical Fellowship Board of the National Research Council about March 1, 1938. Applications must be filed with the secretary of the board, 2101 Constitution Avenue, Washington, D. C., on or before Jan. 1, 1938.

New Commission to Study Cancer.—The legislature of the State of New York has established a commission to survey the prevalence of cancer in the state and the facilities for treatment. The commission, of which James Ewing is a member, will report to the legislature in 1938.

Ella Sachs Plotz Foundation.—During its thirteenth year this foundation received ninety-two applications and made thirty grants, eighteen of which were to investigators outside the United States. The maximum size of the grants is usually less than $500. The secretary is Dr. J. C. Aub, 695 Huntington Avenue, Boston.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Effects of Sodium Amytal and Other Drugs on the Reactivity of the Hypothalamus of the Cat. J. H. Masserman, Arch. Neurol. & Psychiat. **37**:617, 1937.

Masserman investigated the effects of faradization of the anterior portion of the hypothalamus and of the motor cortex in cats and the modifications the reactions undergo after injections of sodium amytal intravenously, intraperitoneally or into the hypothalamus itself. Some of the conclusions arrived at were that very mild faradization of the anterior portion of the hypothalamus produced manifestations resembling those of fear or rage (mydriasis, raising of hair and whiskers, extrusion of the claws, etc.). The reactions occurred in cats that had been unanesthetized or kept under light ether anesthesia. The reactions, both emotional and sympathetic, were somewhat less intense after intravenous or intraperitoneal injections of sodium amytal, while direct injections into the anterior portion of the hypothalamus caused a fall in the blood pressure, also changes in the respiratory rate, but did not otherwise modify its reactivity.

G. B. Hassin.

Vasodilation in the Pia Following Stimulation of the Geniculate Ganglion. H. S. Forbes, G. I. Nason, S. Cobb and R. C. Wortman, Arch. Neurol. & Psychiat. **37**:776, 1937.

The authors tried to determine from experiments on cats whether there are true dilator nerve fibers in the pial blood vessels. They cut the facial nerve between the geniculate ganglion and the internal auditory meatus and stimulated the distal sector by a weak electric current. The effect on the pial circulation was watched through a window over the posterior parietal region of the cortex. They found that after a latent period of about ten seconds the arteries became dilated, reached their maximum size in about twenty seconds and slowly regained their original caliber. The majority of the animals maintained a comparatively high blood pressure, so that the influence of low blood pressure or of a fall in blood pressure, which also may cause dilatation of pial arteries, could be excluded. The reaction on the pial arteries was ipsilateral and could be abolished by irrigating locally over the pial arteries with 1 per cent solution of cocaine hydrochloride. The conclusion seems to be warranted that higher animals (cats and monkeys) possess true vasodilator nerves for the arteries supplying the parietal cerebral cortex. Such nerve fibers come from the medulla and reach the pial blood vessels through the facial nerve, the great superficial petrosal nerve and (in monkeys) the internal carotid nerves.

G. B. Hassin.

Experimental Lymphatic Blockage. A. Blalock and others, Arch. Surg. **34**:1049, 1937.

Complete lymphatic blockage was produced in three dogs by blocking the lymphatic ducts in the neck and chest and by destroying the cisterna and interfering with the drainage of the mesenteric lymphatics. There was almost complete disappearance of lymphocytes and eosinophils from the blood stream. The animals lost weight rapidly. At autopsy the lymphatics of the abdominal organs were markedly distended, and there was extravasation of chyle into many of the tissues. No lymphaticovenous communications were demonstrated.

CUTANEOUS LYMPHATICS UNDER NORMAL AND PATHOLOGIC CONDITIONS. P. D. McMASTER, J. Exper. Med. **65**:347 and 383, 1937.

Vital dyes injected intradermally enter lymphatic capillaries directly, rendering them visible, and appear later in the draining lymphatic trunks as colored streamers. This enables one to perceive the state of the lymphatic channels and the rate of lymph flow within them. The method yields consistent results when tested under physiologic conditions known to increase or decrease lymph flow. In the horizontally placed normal limb at rest there is slight lymph flow. In a normal leg or arm hanging downward lymph flow ceases, although fluid in the limb increases. When a previously dependent arm is raised above the head, or when the foot of a seated subject is propped on a table, lymph flow in the raised limb becomes active. It ceases in the skin of an arm subjected to partial obstruction of the veins by pressure from without, but very active lymph flow appears during the reactive hyperemia which follows release of the venous obstruction. It is still greater following release of obstruction to the total circulation and seems to be the same whether or not the limb was previously engorged with blood. In the ischemic patches which appear in the skin of a limb during obstruction to the total circulation (Bier's spots) the lymphatic capillaries are definitely and considerably constricted, whereas they are slightly dilated in the purple, congested regions of the skin round about. On release of the obstruction there occurs a strikingly rapid equal lymphatic drainage from both regions. The significance of all the findings is discussed. When dye is injected intradermally and the skin sucked, much of the foreign material is driven into the lymphaticsc draining the area.

Local intradermal injections of dye have disclosed the fact that the lymphatics of the skin in regions of cardiac edema are patent, full of fluid and much widened. Intercommunication between them is ready, and dye escapes from them more rapidly than from the vessels of normal skin. A retrograde distribution of dye by way of the lymphatics often occurs, and the dye may pass unseen along the deeper channels to emerge in the skin at unexpected distant situations. Valvular incompetence of the lymphatics consequent on dilatation appears to be the cause of such phenomena. In regions of cardiac edema lymph stagnates, despite the fact that the channels are open. In nephritic edema the lymphatic capillaries are wider than normal but not as wide as in cardiac edema. No sign of incompetency of the valves is to be observed. Instead, lymph flow is considerably greater than normal, even when edema fluid is accumulating. It was noted to be greater in the periods of fluid equilibrium also and extraordinarily rapid in periods of diuresis.

FROM THE AUTHOR'S SUMMARIES.

LIVER FUNCTION AND BLOOD PLASMA PROTEIN FORMATION. R. E. KNUTTI and others, J. Exper. Med. **65**:455, 1937.

Normal dogs and two in which Eck fistulas were produced received a daily diet containing on the average 1 Gm. of vegetable protein per kilogram of body weight. After average intervals of seven to nine weeks, slight decreases appeared in the amounts of circulating plasma protein. A third dog with an Eck fistula under similar circumstances was unable to maintain the concentration of protein in the plasma above the edema level. This dog by biopsy was shown to have an abnormal liver. The evidence indicated that the other organs were normal. The animal showed active thirst and diuresis as compared with controls. This dog had less than a tenth of the capacity of the normal dog to form new plasma protein when various food proteins were added to the basal diet, and no significant quantitative differences in the relative potency of these foods (liver, kidney, heart muscle, soy bean, salmon) could be distinguished. It appears that the abnormality of the liver was responsible for this abnormal reaction. This observation gives strong support to the thesis that the liver is actively concerned with fabrication of new plasma protein.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL RENAL LESIONS AND BLOOD PRESSURE IN RABBITS. R. W. SCARFF and M. MCGEORGE, Brit. J. Exper. Path. **18**:59, 1937.

Experiments are described in which the blood pressure in rabbits was read after various renal injuries; these injuries included oxalate nephritis, unilateral and bilateral nephrectomy, trauma, ligation of ureters and glomerular embolism induced with inert material and with killed bacteria in sensitized animals. In many of the animals considerable impairment in renal function was indicated by an increase in the blood urea, but in none of them was there any significant rise in the blood pressure.

FROM THE AUTHORS' SUMMARY.

RESISTANCE TO POSTERIOR PITUITARY IN DIABETES INSIPIDUS. J. H. BIGGART, J. Path. & Bact. **44**:305, 1937.

Two cases of diabetes insipidus refractory to the antidiuretic factor are recorded. It is suggested that in the human subject damage to the tuberal nuclei, with or perhaps without concomitant damage to the supra-opticohypophysial system, results in a form of diabetes insipidus which is not controlled by the antidiuretic factor.

FROM THE AUTHOR'S SUMMARY.

CHANGES INDUCED BY ESTROGENIC SUBSTANCE IN THE BULBO-URETHRAL GLAND OF THE MALE MOUSE. H. BURROWS, J. Path. & Bact. **44**:481, 1937.

Continued administration of estrogenic substance to the male mouse causes an epithelial metaplasia in the duct and body of the bulbo-urethral gland. This metaplasia starts at the entrance of the duct into the urethra after metaplasia in the urethra has already occurred and then gradually spreads through the duct and body of the gland. Cystic dilatation and suppuration may appear as complications.

FROM THE AUTHOR'S SUMMARY.

CHRONIC INFLAMMATORY AND SCLEROTIC PROCESSES IN THE THYROID GLAND. B. BASTENIE, Arch. internat. de méd. expér. **12**:1, 1937.

Histologic analysis of specimens collected in cases of atrophic thyroiditis, myxedema, Riedel's struma and diffuse lymphoid thyroiditis (Hashimoto) show all of these conditions to have in common a primary degenerative change in the glandular epithelium. Depending on whether lymphoid reaction, progressive diffuse interstitial fibrosis or dense focal scarring makes up the dominant eventual picture, various forms of thyroiditis result. More localized areas of inflammatory reaction or scarring are found secondary to focal epithelial degeneration in simple goiters, nodular goiters, exophthalmic goiters and in thyroid glands obtained at necropsy. Inflammatory changes are rarely encountered in pure exophthalmic goiter but are frequent in partial involution induced by iodine. Degenerative changes are most evident in focal compact aggregations of epithelial cells or nests of small acini. These are apparently areas of incomplete or abnormal involution.

Degenerative and chronic inflammatory changes in the thyroid gland fall into two main groups. The first includes processes in which there is an element of endocrine stimulation of the gland; in this group are essential hypertension, Addison's disease and ovarian dysfunction. The second group comprises processes essentially of nutritional character, such as obesity, cholelithiasis, diabetes, pellagra and hyperchromic anemia. Intense fibrosis occurs almost constantly in pellagra and in hyperchromic anemia. It seems probable that deficiency states may result in inflammatory changes in the thyroid gland without necessarily leading to the syndrome of pellagra or to hyperchromic anemia.

Animal experiments tend to corroborate the conclusions based on clinical and anatomic analysis. The thyroid glands of young rats on an ordinary unrestricted diet do not show lymphocytic infiltration or interstitial fibrosis. In only a small percentage of guinea-pigs are inflammatory changes found in the thyroid glands. Thyroids with focal compact masses of epithelial cells with degenerative change

and small perivascular accumulations of lymphocytes are found only in old or pregnant animals. Degenerative and inflammatory changes are not induced by the administration of diphtheria or streptococcus toxins. Infectious disease does not affect the incidence of such lesions. Acute hyperactivation of the thyroid gland by thyrotropic hormone produces a picture analogous to that of thyroid hyperactivity in man, without lymphocytic infiltration or scarring. Rats on the McCarrison deficiency diet show arrest of growth, loss of weight, dehydration, enteritis, hemorrhage from the intestine and dermatitis. The thyroid glands of these animals show atrophic acini and marked interstitial fibrosis without inflammatory infiltration. Similar results are obtained by restricting the animals to a diet of bread and water during the winter. Repetition of such a regimen during the summer months leads to degenerative changes with lymphocytic infiltration. Addition of iodine to the diets increases the development of lesions. A diet of beets, hay and bread results in both degeneration and inflammatory reaction in the thyroid gland, and administration of thyrotropic hormone appears to intensify the lesions produced.

The theory is developed that chronic thyroiditis is secondary to degenerative changes in the glandular epithelium. In the production of the primary degenerative change a number of factors seem important: (*a*) a constitutional factor, (*b*) the various processes which may lead to endocrine stimulation of the thyroid gland, (*c*) vitamin deficiency and (*d*) possibly physical or geographic factors, such as temperature, radiant energy and the ingestion of iodine. RALPH H. FULLER.

ROENTGEN-KINEMATOGRAPHIC STUDIES OF THE EFFECTS OF ELECTRICAL CURRENTS ON THE RESPIRATION AND CIRCULATION OF ANIMALS. F. PIETRUSKY and R. JANKER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **28**:347, 1937.

In narcotized cats and guinea-pigs a study was made of the effects on the heart, vascular system and lungs of the passage of an electrical current. It is well known that the results of the passage of electrical currents vary widely in various species of animals and in individual animals as well. In two cats, the vessels were rendered visible by injections of thorium dioxide. Alternating current of varying cycles, voltage and amperage was used. The same contacts were used in each experiment: the left front paw and the right hind paw.

In one cat a current of 250 volts, 0.5 amperes and 50 cycles was used for six seconds. At the moment the current was applied, the animal bent forward and both sides of the diaphragm rose and remained in a position of expiration. The inferior vena cava became broad, the auricles wide, and the ventricles remained contracted. The right auricle fluttered slightly. When the current was stopped, no changes occurred for twelve seconds; then a flutter started in the left ventricle, then in the right, and finally in the auricles. Respirations began in twenty-four seconds and were slow and deep, with the diaphragm contracting maximally. After forty seconds, the cardiac action ceased, and the animal died.

Representative roentgen films portrayed the course of events, as eighteen pictures were taken per second. The current used in one cat was of 240 volts, 0.5 amperes and 500 cycles per minute. In the guinea-pig it was 1,000 volts, 1 ampere and 50 cycles. The variations in reaction after single and after repeated shocks are painstakingly portrayed. GEORGE RUKSTINAT.

Pathologic Anatomy

THE PANETH CELL. A. J. HERTZOG, Am. J. Path. **13**:351, 1937.

Paneth cells are coarsely granular cells found constantly in the small intestine of man. They are most numerous in the jejunum and ileum, where they are present in practically equal numbers. They occur less frequently in the duodenum. Paneth cells may occur occasionally in the colon and appendix, also in the stomach, under pathologic conditions. Age and sex do not influence their occurrence. The granules are easily preserved by ordinary fixatives. The Paneth cell gives evidence of being mucoid rather than an independent zymogenic cell.

FROM THE AUTHOR'S CONCLUSIONS.

THE CORTICAL ATROPHY IN DEMENTIA PARALYTICA. H. H. MERRITT, T. J. PUTNAM and A. C. P. CAMPBELL, Arch. Neurol. & Psychiat. **37**:75, 1937.

It is held that the cortical atrophy in dementia paralytica is explained by anorexia from capillary changes. Hyperplasia of the endothelium of the capillaries causes narrowing and obstruction of the lumen, resulting in deficient nutrition and atrophy of the cerebral parenchyma. The atrophied areas in dementia paralytica contain fewer small blood vessels than corresponding normal areas. Experiments on dogs in which an isolated sector of the longitudinal sinus was given an injection of shellac seemed to support the authors' hypothesis, the brains in two or three weeks presenting changes ordinarily found in dementia paralytica: meningeal round cell infiltrations, infiltrations of the cortical blood vessels with microglia cells and occasional lymphocytes, endarteritis, iron pigment in the walls of some of the blood vessels and rod cells with circumscribed loss of myelin in the white matter.

G. B. HASSIN.

DIABETIC COMA AND ACUTE PANCREATITIS WITH FATTY LIVER. H. F. ROOT, J. A. M. A. **108**:777, 1937.

Acute pancreatitis that was unsuspected during life was found to be the cause of death in four of twenty-six cases in which death occurred during or after recovery from diabetic coma. Causes of death in diabetic coma cannot be ascertained, and statements regarding the efficiency of treatment should not be made without the knowledge afforded by postmortem examination. Acute pancreatitis must be searched for in every case of severe diabetic coma, and the differential diagnosis should include acute hepatitis, perforated ulcer and acute cholecystitis, as well as the other causes of acute symptoms in the upper part of the abdomen. Lipemia occurred in the only one of the four patients for whom an analysis of the blood was made. Lipoid infiltration of the liver, with enlargement of the latter, occurred in all four cases.

FROM THE AUTHOR'S SUMMARY.

AN ANALYSIS OF MITOSIS IN LIVER RESTORATION. A. M. BRUES and B. B. MARBLE, J. Exper. Med. **65**:15, 1937.

Following partial hepatectomy in the rat, there is a latent period of one day during which the rapidly growing organ shows no increase in cell number. Mitosis then begins rapidly, following a brief premitotic period of visible nuclear changes. It can be shown that the increase in cell number during the ensuing forty-eight hours follows a formula of the type $dN/dt = ke^{-kt}$; beyond this time it is retarded more than this simplified formula would predict. The average rate of mitosis at one, two and three day intervals after operation follows the same formula; from this the duration of each mitosis is calculated to be about forty-nine minutes. It is not necessary to assume that amitotic division plays an imporant part, and no such divisions have been seen by the writers. The percentage of cells in mitosis in a single hypertrophying liver varies widely from hour to hour, so that a single count of mitoses tells nothing about the rate of growth. The fluctuations occur at different times in different livers. It appears that no great number of mitoses begin or end simultaneously. Mitoses are evenly distributed throughout the liver and throughout each lobule; there is no preponderance near the bile duct cells. The mean initial rate of mitosis (twenty-four hours after operation) is 2.13 per cent, and it diminishes from then on. This rate is very similar to that in early embryo heart and in tissue cultures of mesenchyme. In individual specimens the rate can be over 8 per cent. This rapid rate occurs without signs of cell dedifferentiation.

FROM THE AUTHORS' SUMMARY.

THE CAPILLARY SUPPLY IN NORMAL AND HYPERTROPHIED HEARTS OF RABBITS. R. A. SHIPLEY, L. J. SHIPLEY and J. T. WEARN, J. Exper. Med. **65**:29, 1937.

During normal growth of the rabbit's heart, the muscle fibers enlarge, and the capillaries multiply so that a relatively constant capillary supply per unit of tissue

is maintained from the time of birth to maturity. In cardiac hypertrophy the muscle fibers enlarge, but the capillaries do not multiply and, as a result, the capillary supply per unit of tissue is reduced. The decreased concentration of capillaries in the hypertrophied heart would constitute an impediment to the adequate exchange of metabolic substances, but the seriousness of the impediment cannot be estimated without further physiologic data.

FROM THE AUTHORS' SUMMARY.

MULTIPLE NECROSIS OF THE SPLEEN (SPECKLED SPLEEN). H. A. MAGNUS, J. Path. & Bact. **44**:103, 1937.

Two cases of multiple necrosis of the spleen are described. The literature is surveyed, and an etiologic classification of the condition into four groups, arteriosclerotic-toxic-thrombotic, toxic-thrombotic, toxic, and arteritic is suggested.

FROM THE AUTHOR'S SUMMARY.

MASSIVE NECROSIS OF THE LIVER FOLLOWING INTRAPORTAL ADMINISTRATION OF POISONS. G. R. CAMERON, W. A. E. KARUNARATNE and J. C. THOMAS, J. Path. & Bact. **44**:297, 1937.

Many organic poisons when introduced directly into the portal circulation produce massive areas of necrosis. This effect is not due to embolism or to any form of ischemia but to direct action of the poison on the liver cells. The condition may be called "toxic infarction."

FROM THE AUTHORS' SUMMARY.

GLYCOGEN IN HUMAN TESTICLE. E. VON GIERKE, Beitr. z. path. Anat. u. z. allg. Path. **98**:351, 1937.

Testicular tissue was fixed for twenty-four hours in a solution of formaldehyde, dehydrated with alcohol and embedded in pyroxylin (celloidin). Staining was carried out by the carmine method of Best, modified to eliminate abnormal deposits of the dye in the sections. Von Gierke confirmed his earlier experience that the demonstration of glycogen in tissues by no means depends on the absolute freshness of the tissues and that prolonged fixation in formaldehyde does not essentially influence staining. Furthermore, the time between death and autopsy does not seem to play an important rôle. Glycogen was a frequent finding in the human testicle. It was most abundant when the seminal epithelial cells were in the resting stage, disappearing with the development of sperms. It is supposed that glycogen is consumed by the seminal epithelial cells during spermatogenesis. The largest amounts of glycogen tended to occur in diabetes mellitus.

R. J. LEBOWICH.

BASOPHILIC DEGENERATION OF CARDIAC MUSCLE FIBERS. G. LIEBEGOTT, Beitr. z. path. Anat. u. z. allg. Path. **98**:410, 1937.

The previous observations of a peculiar change in heart muscle fibers termed basophilic degeneration by Haumeder are confirmed. This degeneration first takes place in the immediate vicinity of the nuclear poles of the muscle fibers and extends from them for a short and variable distance. In hematoxylin-eosin preparations, the degeneration is vacuolar, with destruction of muscle fibers, deposition of scattered granules of a brown pigment, development of blue staining and, as a rule, the appearance of poorly outlined irregular minute foci. The nuclei of the affected fibers are displaced eccentrically and only rarely appear to be hypertrophied. Age, sex, occupation and disease throw no light on the blue-staining foci of degeneration. The belief that they may represent a postmortem autolysis is rejected. Their origin is explained on the basis of intravital regressive processes or on that of an intermediate postmortem reaction.

R. J. LEBOWICH.

INCREASING INCIDENCE OF FATAL THROMBOTIC PULMONARY EMBOLISM. F. PRETTIN, Virchows Arch. f. path. Anat. **297**:535, 1936.

A number of writers have noted an increase in the number of deaths due to pulmonary embolism since 1926 as determined from necropsy material. Some authors have criticized this finding because the mean deviation was not taken into account. Prettin made a statistical analysis of deaths due to pulmonary embolism in the necropsy material of the pathologic institute of Rostock for the years from 1932 to 1935, inclusive. A similar analysis had been made in the same institute by Höring for the period from 1922 to September 1927, inclusive, and by Damblé for that from September 1927 to April 1931. In 1932-1935 there were 2,897 necropsies, with a yearly mean of deaths due to pulmonary embolism of 7.69 ± 1.47 per cent. For the period from 1922 to September 1927 the figure was 4 ± 1.05 per cent, and for that from September 1927 to April 1931 it was 4.2 ± 1.25 per cent. The author holds that his analysis reveals a significant increase. Two thirds of all fatal pulmonary embolisms were not diagnosed before necropsy. Most often postoperative pulmonary embolism occurred between the third and the eighth day after operation. There was a significant increase in the number of posttraumatic pulmonary embolisms; most often the embolism occurred in the interval from the eighth to the fifteenth day. Postoperative embolism was most common after operations below the diaphragm. Most often the thrombus that led to embolism was primary in the veins of the lower half of the body. No difference in the predisposition of the two sexes was observed. Eighty-eight per cent of the fatal embolisms occurred in persons over 40 years of age; there was a progressive increase in each decade above the fifth. A seasonal relationship was not evident. More than half of the persons who died of pulmonary embolism had disease of the circulatory system. The average weight of women dying of pulmonary embolism was 11 Kg. greater than that of women of the same age groups dying of other diseases; in men the weight difference was 4.2 Kg.

O. T. SCHULTZ.

INVOLVEMENT OF THE GASTRO-INTESTINAL TRACT IN LEUKEMIA AND SIMILAR DISORDERS. A. OTT, Virchows Arch. f. path. Anat. **297**:548, 1936.

A systematic study was made of the frequency and degree of involvement of the gastro-intestinal tract in the leukemia and similar diseases. Under leukemias are included the acute and chronic lymphoid and myeloid forms, the monocytoses and the reticuloses. The similar diseases considered are lymphosarcomatosis and lymphogranulomatosis. In the various forms of leukemia leukemic infiltration of the gastro-intestinal tract is almost universally present. It is more marked in the stomach than in the intestine, in chronic than in acute forms, in persons of middle and advanced age than in young persons, and in men than in women. The leukocyte count in the cases in which leukemic infiltration was most marked was only moderately elevated. In younger persons gastro-intestinal involvement was encountered more often in lymphosarcomatosis and lymphogranulomatosis than in the leukemias.

O. T. SCHULTZ.

Microbiology and Parasitology

INFLUENCE OF VARIATIONS IN EXPOSURE IN AMEBIASIS. A. V. HARDY, Am. J. Hyg. **25**:421, 1937.

Two groups of Chicago residents were observed, one exposed to polluted water on one day only, the other repeatedly during a period of over five months. There was no significant difference in the proportion found to have been infested with Endamoeba histolytica, but there was the broadest difference in the incidence of amebic dysentery. The resident guests of the two hotels which were involved in the epidemic of amebic dysentery were exposed for varying periods. The incidence of amebic dysentery was found to vary directly and approximately proportionally with the duration of exposure. FROM THE AUTHOR'S SUMMARY.

SIMILARITY OF LESIONS PRODUCED BY SILICA AND BY THE TUBERCLE BACILLUS. L. U. GARDNER, Am. J. Path. **13**:13, 1937.

This study has confirmed the specificity of the tuberculin reaction and has again demonstrated that the mere presence of a pseudotubercle composed of epithelioid cells does not create hypersensitiveness to tuberculin. Silica itself is not antigenic, and intracutaneous injections produce the same effects in silicotic and in normal control animals.

THE PROBLEM OF INFECTION PRESENTED BY BACTERIAL INVASION OF THE CHORIO-ALLANTOIC MEMBRANE OF CHICK EMBRYOS. E. W. GOODPASTURE and K. ANDERSON, Am. J. Path. **13**:149, 1937.

Inoculation of the chorio-allantoic membrane of the chick embryo with a pure culture of a pathogenic bacterium is a practical method for studying problematic phases of infection, especially the early stages of invasion. It is indicated in this survey of the use of the method that many pathogenic bacteria find in mesodermal cells (fixed or mobile), epithelial cells or both favorable and possibly necessary mediums for invasion of the living host. In these instances phagocytosis, instead of representing resistance to infection, actually favors it. Among pathogenic bacteria that are able to utilize a living intracellular environment for growth are Streptococcus viridans, Aerobacter aerogenes, Eberthella typhi, Brucella abortus and Mycobacterium tuberculosis-avium. Staphylococcus aureus and Streptococcus haemolyticus may be in part destroyed by the phagocytes of the embryo, and they appear to be incapable of growing in an intracellular medium in this host.

FROM THE AUTHORS' SUMMARY.

THE BEHAVIOR OF TUBERCLE BACILLI WITHIN THE BODY. H. J. CORPER, M. L. COHN and A. P. DAMEROW, Am. Rev. Tuberc. **33**:679, 694, 701, 709 and 721, 1936.

This series of articles, based on accurate quantitative studies with various strains of tubercle bacilli to discern their effects when introduced by various routes into four species of animals, shows that there is a definite quantitative relation between pathogenicity and virulence in the species susceptible to infection with a specific virulent strain. The bacilli may remain viable in the body for months, even in the absence of multiplication. Following the injection of viable virulent or avirulent bacilli there is a striking relative difference in the second virulent infection. The protective effect requires a certain time to develop and exerts no apparent retro-active effect. Nonviable (heat-killed) avirulent or virulent bacilli produce no such protective effect. Avirulent human and bovine tubercle bacilli in relatively large amounts (5 mg.) given intravenously produce no definite gross tuberculous changes in guinea-pigs, while virulent bacilli to the amount of less than a millionth part mixed with the avirulent bacilli are readily disclosed. The immune effect is produced definitely when macroscopic tubercles are produced by the intracutaneous injection of avirulent tubercle bacilli, but there is no evidence of multiplication of the latter. No evidence of ready change from virulence to avirulence or vice versa was noted. A certain immune specificity of the human and bovine strains was noted.

H. J. CORPER.

RÔLE OF NON-ACID-FAST RODS AND GRANULES IN THE DEVELOPMENTAL CYCLE OF THE TUBERCLE BACILLUS. M. C. KAHN and J. F. NONIDEZ, Am. Rev. Tuberc. **34**:361, 1936.

The peripheral zones of the colonies of the tubercle bacillus are held to be the younger and to be zones of active growth for these reasons: I. Nonacid-fast small forms are abundant here in young colonies, and in old colonies which have ceased to grow the peripheral zone is almost entirely obliterated, there being only a few nonacid-fast forms among strongly acid-fast rods. 2. A young thin mem-

branous growth on Long's liquid medium reveals nonacid-fast granules and rods. 3. The myobacteria at the periphery of the colony are presumably receiving the most oxygen. 4. Studies of single cells indicate that the nonacid-fast granules and rods are the youngest forms.

The developmental cycle is a type of segmentation rather than of direct fission. The bodies become increasingly numerous as they become smaller. The loss of acid-fastness in the granule and small rod phase may possibly be explained on a metabolic basis; the potential of elongation does not keep pace with the potential of division, and at certain stages there is seemingly insufficient time for the organisms to metabolize the substances essential to their acid-fastness. When the potential of division becomes less, the individual granule has more opportunity for growth or elongation and for metabolizing the chemicals necessary to acid-fastness. The cycle described takes place when conditions are favorable, but this is not the only means of reproduction; others may take place, and direct fission in the usual sense of the word may well be one of these.

H. J. Corper.

Experimental Study of Congenital Syphilis. J. E. Kemp and P. D. Rosahn, Bull. Johns Hopkins Hosp. **60**:45, 1937.

In five pregnant rabbits with early syphilis treponemes were found in the blood, uteri and placentas. However, no evidence of infection was found in forty-seven fetuses from twelve pregnant rabbits with early syphilis. It appears that either the placenta forms a barrier to the spread of the infection from the syphilitic female rabbit to her offspring or the treponemes are destroyed after reaching the fetus. Furthermore, there was no difference in susceptibility to infection between the offspring of normal and syphilitic mothers. No difference in the development or viability of the two groups of young was noted that could not be explained by the limitations of the laboratory facilities for the breeding of animals.

From the Authors' Conclusions.

Postoperative Bacteroides Infection. C. F. Dixon and J. L. Deuterman, J. A. M. A. **108**:181, 1937.

In six cases of infection with Bacteroides funduliformis infection occurred after operation for carcinoma of the colon. Only one of the six patients recovered, the mortality therefore being 83 per cent. At necropsy, multiple abscesses were found in the liver in every case in which death occurred. Blood culture for B. funduliformis should be made in cases in which icterus occurs after operation, even though other signs of septicemia may not be present. Early cultures for anaerobic bacteria should be made of material from the wound and of the blood in order to make a diagnosis before death. Specific treatment is not available.

From the Authors' Summary.

The Somatic C Polysaccharide of Pneumococcus. T. J. Abernethy and T. Francis Jr., J. Exper. Med. **65**:59 and 75, 1937.

Cutaneous and Serologic Reactions in Pneumonia (T. J. Abernethy and T. Francis Jr.).—A study of forty-six cases of pneumococcic pneumonia has shown that a characteristic response may be elicited in the patient by intracutaneous injection of 0.1 mg. of the somatic polysaccharide C of the pneumococcus. During the acute febrile period in the patient who recovers, the response consists of a delayed erythema, which reaches its maximum intensity in from eighteen to twenty-four hours. During convalescence such a reaction is not demonstrable. In the patient in whom the disease is prolonged by complications the capacity of the skin to react persists. In seven fatal cases the skin failed to react to this polysaccharide. Parallel studies of the reactions of patients' serums with the polysaccharide have confirmed and extended the observations of Tillett and Francis on the appearance of the precipitation phenomenon during the acute stage and its disappearance in

recovery. That the cutaneous and serologic reactions are not specific for pneumococcic infection is shown by the results in twenty-nine control cases. Eight patients with infectious febrile diseases not of pneumococcic origin gave responses similar to those noted in patients with pneumonia. Two patients with noninfectious fevers and eighteen of nineteen normal persons failed to give either skin or serum reactions. These observations emphasize the importance of using separate components of the bacterial cell in the interpretation of cutaneous and serologic reactions in pneumonia. The parallelism in the results of the skin and serum tests with the somatic carbohydrate C in pneumococcic pneumonia, the significance of the reactions in relation to the clinical course and outcome of the disease and the frequency of occurrence of both reactions in bacterial infections other than those of pneumococcic origin are discussed.

Precipitation Reaction in Animals with Experimentally Induced Pneumococcic Infection (T. J. Abernethy).—The capacity of the serums of rabbits following intradermal pneumococcic infections to give a precipitate in the presence of polysaccharide C has been studied during the resultant periods of active infection and recovery. In rabbits infected with pneumococci of type I, III or VIII large hemorrhagic lesions are produced, which frequently bring about death of the animals after a febrile illness of from three to four days. Repeated precipitation tests with the serums of these animals have been uniformly and consistently negative, not only during the acute illness but in the period of recovery as well. On the other hand, the serums of monkeys (Macacus cynomolgos) actively ill with experimental type III pneumonia have been shown to react in precipitation tests with the C substance. The serum reaction appears within the first twenty-four hours after infection, remains positive in high titer for from two to three days during the acute illness and disappears with the onset of recovery. The precipitation reaction polysaccharide C also occurs in the serums of monkeys following intradermal and intraperitoneal infection with pneumococci. The results of precipitation tests of the serums of monkeys during experimental pneumonia are similar to those obtained with the serums of patients suffering from pneumococcic lobar pneumonia. From the results of these studies it appears improbable that the demonstration of the serum precipitation phenomenon with polysaccharide C in monkeys, and possibly also in man, is conditioned by previous exposure to pneumococcus antigens.

FROM THE AUTHORS' SUMMARIES.

CLIMATE AND THE STREPTOCOCCUS-RHEUMATISM RELATIONSHIP. W. B. SHARP and M. B. JOHN, J. Infect. Dis. **60**:15, 1937.

The rate of admission to hospitals of patients with acute rheumatic affections is found to be about 15 per cent as high in Galveston, Texas, as in Chicago. The southern climate tends in this degree to prevent or mitigate attacks of rheumatism. The influence reaches its peak in the summer but is pronounced throughout the year. The carriage of hemolytic streptococci is at a low level during the summer but not throughout the year, like rheumatism. The incidence of uncomplicated rheumatic fever is cut to 28 per cent and that of Sydenham's chorea to 3 per cent of the northern figure. This disparity between the two forms of rheumatic attack would not be expected if the lowering of incidence were solely in response to the lighter exposure to streptococci.

The observations indicate that diminution in the carriage of streptococci is not the likely medium of control over rheumatic attacks.

FROM THE AUTHORS' SUMMARY.

THE MORPHOLOGY OF HAEMOPHILUS PERTUSSIS. J. A. TOOMEY and W. S. TAKACS, J. Infect. Dis. **60**:41, 1937.

Morphologic changes occur in Haemophilus pertussis on all mediums, on some relatively later than on others. When the organism is grown on hemoglobin blood agar (p_H 6 to 6.4, as modified by Povitzky) it may retain its characteristics

as long as two years. Acclimated to and grown on a medium without blood it quickly becomes bacillary, often as early as the first successful transplanting. If grown too long on a medium without blood, it becomes fixed in type in that nothing that these workers have done thus far has endowed the organism with disease-producing characteristics. FROM THE AUTHORS' CONCLUSIONS.

NECESSITY OF LIVING CELLS FOR THE CULTIVATION OF PSITTACOSIS VIRUS. F. O. MACCALLUM, Brit. J. Exper. Path. **17**:472, 1936.

The evidence presented in this paper supports the view that the virus of psittacosis is an obligate intracellular parasite.

FROM THE AUTHOR'S SUMMARY.

OBSERVATIONS ON THE ETIOLOGY OF INFLUENZA. R. W. FAIRBROTHER and L. HOYLE, J. Path. & Bact. **44**:213, 1937.

Attempts by inoculation of ferrets to isolate a virus from sporadic cases of influenza and other diseases in an interval between epidemics in the Manchester district have given negative results. Studies of normal human serums in this area have shown that neutralizing antibodies against the viruses of both human and swine influenza are present in many of them. A complement fixation test has been developed for the study of the antibody content of human serums, and the results obtained indicate the presence of a common antigenic factor in the human and swine viruses. The antigen concerned with complement fixation is distinct from that involved in the neutralization test. Attempts to isolate virus from material collected during an outbreak of epidemic influenza in Leningrad have given negative results. This may be explained by the delay in transit of the material. A small number of serums collected after the epidemic provided some evidence that the virus may have been the causal agent.

FROM THE AUTHORS' SUMMARY.

PATHOGENESIS OF NEUROSYPHILIS. C. LEVADITI, A. VAISMAN and R. SCHOEN, Ann. Inst. Pasteur **56**:481, 1936.

Spirochaeta pallida, after from six to twenty days in the axons of rabbits, failed to induce scrotal syphiloma in new rabbits. The reverse was also observed. It appeared probable that the factors which facilitate the start of parasyphilis are represented by the anallergic changes in the receptivity of the central nervous system. The general picture indicated great difficulty in adaptation of the virus to the axon on direct introduction into the brain. M. S. MARSHALL.

EYE AND NERVOUS SYSTEM IN LEISHMANIASIS. S. NICOLAU and C. PÉRARD, Ann. Inst. Pasteur **57**:463, 1936.

The results show that the eyes of dogs infected with Leishmania, intact in appearance, are invaded by organisms to an extent which may result in blindness. Alterations in the meninges, encephalic ventricles, metencephalic parenchyma, spinal ganglions, nerve roots and peripheral nerves explain the nervous symptoms in certain cases of leishmaniasis. FROM THE AUTHORS' CONCLUSIONS.

MORPHOLOGIC INVESTIGATIONS OF BRESLAU INFECTION IN VACCINATED RABBITS. A. WALDMANN, Zentralbl. f. Bakt. (Abt. 1) **137**:45, 1936.

Rabbits were immunized against Bacterium enteritidis Breslau by intravenous, subcutaneous, intratracheal, intragastric and intraduodenal injection of vaccines killed by heat or solution of formaldehyde. Later, these animals, with controls, were infected by introducing into the duodenum of each, through a small abdominal incision, living bacilli of the same strain. The infection was then followed, and

the pathologic changes were observed. Most of the normal rabbits died within from four to five days, and autopsy revealed hyperplasia and necrosis of Peyer's patches and of mesenteric lymph nodes. On the other hand, vaccination by any of the routes was followed by a much higher survival rate after subsequent intraduodenal infection. The highest percentages of survival were of rabbits immunized intraduodenally or intratracheally, but the number of animals is too small for the results to be conclusive. Practically all of the vaccinated animals showed lesions in the Peyer's patches which were similar qualitatively to those in the normal controls. It is of interest that the animals which were immunized intraduodenally had extremely low agglutination titers for the blood serum and yet resisted intraduodenal infection well, illustrating the lack of any direct relationship between agglutination titer of serum and grade of immunity. The least successful immunization was of the animals vaccinated intragastrically. PAUL R. CANNON.

ACUTE ATYPICAL MILIARY TUBERCULOSIS. F. HARBITZ, Acta tuberc. Scandinav. **10**:59, 1936.

Attention is directed to acute forms of tuberculosis which present in their clinical course an indefinite, mostly septic picture, and in which only microscopic examination reveals that there is present a kind of atypical miliary tuberculosis. At the same time there is present a blood picture resembling lymphatic leukemia, which is assumed to stand in direct etiologic connection with the tuberculosis.

FROM THE AUTHOR'S SUMMARY.

Immunology

TETANUS IMMUNITY. P. A. T. SNEATH, E. G. KERSLAKE and F. SCRUBY, Am. J. Hyg. **25**:464, 1937.

Computable numbers of the spores of Clostridium tetani have been shown to induce lethal tetanus in unprotected guinea-pigs when mixed with a 50 per cent solution of calcium chloride and injected intramuscularly. This has been designated a lethal dose. Within from four to eight weeks after being given injections of tetanus toxoid guinea-pigs are more effectively protected from death and other signs of tetanus following administration of the lethal spore dose than animals similarly infected and passively protected by a single dose of tetanus antitoxin. In two groups, each of fifty-five animals, it was found that of the actively immunized ones, 9 per cent died of tetanus and 8 per cent were completely protected, whereas, of the passively protected ones, 38 per cent died and 24 per cent were completely protected. An antitoxin level of approximately 0.01 unit per cubic centimeter of serum appears to be the critical level, desirable of attainment, in active immunization of guinea-pigs. Since infection with Cl. tetani is a localized process, it is probable that the level of antitoxin which will prevent manifestations of tetanus in guinea-pigs will also prevent them in man.

FROM THE AUTHORS' SUMMARY.

LEUKEMOID RESPONSE OF TUBERCULOUS RABBITS TO TUBERCULIN. W. H. FELDMAN and J. STASNEY, Am. J. M. Sc. **193**:28, 1937.

In an attempt to obtain experimentally a leukocytic response comparable to the so-called leukemoid reaction described as occasionally associated with tuberculosis in human beings, a group of eleven tuberculous rabbits was studied. The hematologic observations were restricted to the quantitative and qualitative characteristics of the leukocytes. The results indicate definitely that tuberculin given to sensitized rabbits provokes an increase in the number of leukocytes, which is often of striking proportions. This increase is predominantly granulocytic, and there occurs a marked shift to the left. Definite hyperplasia of the bone marrow, mitosis of the immature myeloid cells of the peripheral blood and other significant changes

suggest a condition similar to the leukemoid reaction. The monocytes participate in the leukocytosis rather insignificantly, whereas the lymphocytes show a definite tendency to diminish in number during the reaction. Tuberculin given to nontuberculous rabbits has no significant effect on the leukocyte count.

From the Authors' Summary.

Local Anaphylactic Lesions of the Brain in Guinea-Pigs. L. Alexander and A. C. P. Campbell, Am. J. Path. **13**:229, 1937.

Local anaphylactic lesions were produced in the brains of guinea-pigs sensitized by a single intraperitoneal injection of horse serum by reinjecting the antigen intracerebrally. The symptoms were prolonged or brief convulsions, diminution of activity, ruffling of the hair and scratching at the nose. Brief convulsions and transient ruffling of the hair were occasionally noted also in nonsensitized animals. The anaphylactic lesions were characterized by hemorrhage, vascular thrombosis, necrosis, demineralization, infiltration with neutrophilic polymorphonuclear leukocytes, scavenger cells, microglial and oligodendroglial cells and astrocytes. Anemia, attributed to compression of capillaries by edema, was observed around the lesions. Similar but much smaller lesions were produced in unsensitized guinea-pigs by a single intracerebral injection of the horse serum. The lesions in the sensitized animals differed quantitatively rather than qualitatively from those in the controls. The mechanism of production of the lesions and their possible relation to pathologic changes in man are discussed.

From the Authors' Summary.

Hemolytic Transfusion Reaction Produced by the Blood of a "Universal Donor." E. L. DeGowin, J. A. M. A. **108**:296, 1937.

The injection of 125 cc. of blood from a certain group O donor into a group AB recipient, who was only slightly anemic, produced a severe reaction with evidence of hemolysis in vivo. The donor's blood was found to contain an alpha agglutinin active in a dilution of 1:80 and a corresponding hemolysin active in a dilution of from 1:12 to 1:20. The beta agglutinin was potent only in a dilution of 1:12.

From the Author's Summary.

Tissue Culture Studies on Bacterial Hypersensitivity. J. K. Moen, J. Exper. Med. **64**:943, 1936.

Mononuclear exudative cells obtained from tuberculous guinea-pigs by intrapleural injection of paraffin exhibited characteristic sensitivity to the toxic action of tuberculin when tested in tissue culture. Experiments with these cells, practically free from body fluids, showed conclusively that sensitivity to tuberculin is an inherent characteristic of mesenchymal cells from tuberculous animals. Fibroblastic growths which developed from mononuclear exudative cells derived from a tuberculous animal showed persistence of sensitivity to the toxic action of tuberculin on repeated transplantations in vitro over a prolonged period.

From the Author's Summary.

Does the Gonadotropic Hormone Induce Antibodies or Antihormones? F. Sulman, J. Exper. Med. **65**:1, 1937.

Sulman shows in experiments on rabbits that the purified gonadotropic hormone has no function as an antigen or a haptene whether it is in the form derived from the urine of pregnant women or in the form derived from the blood of pregnant mares. The results reported elsewhere which have led some to ascribe an antigenic structure to the aforementioned hormone from urine are due to confusion of this substance with the so-called nonspecific urinary antigen (urinary colloid). Serums of rabbits which are abundant in an antihormone (Collip) for the substance in question contain no antibodies against it. The antihormones against these

gonadotropic substances must accordingly be considered as protective ferments (Abderhalden). The employment of castrated animals has no influence on the results described. The lack of immunizing components in the pure gonadotropic hormones from the urine of pregnant women and the blood of pregnant mares (*a*) eliminates the possibility of serologic diagnosis of pregnancy for the diagnostician and (*b*) protects the therapeutist against undesirable toxic and allergic secondary effects in intensive treatment with the pure hormones from the urine of pregnant women and the blood of pregnant mares. No antibodies for the former could be found in the blood of pregnant women in the second and fourth month of pregnancy or one day and one month post partum. Antihormone against the substance of human origin has no paralyzing effect on that from the blood of pregnant mares; there exists, therefore, species specificity.

FROM THE AUTHOR'S SUMMARY.

IMMUNIZATION OF RABBITS TO INFECTIOUS PAPILLOMATOSIS. R. E. SHOPE, J. Exper. Med. **65**:219, 1937.

Two intraperitoneal injections of either infectious or noninfectious rabbit papilloma in suspension will actively immunize rabbits against papillomatosis. The capacity of the noninfectious papilloma to immunize is considered as evidence that it contains virus even though none can be demonstrated by the usual test for infection.

FROM THE AUTHOR'S SUMMARY.

AN ANTIGENIC POLYSACCHARIDE OF ASCARIS LUMBRICOIDES (FROM HOG). D. H. CAMPBELL, J. Infect. Dis. **59**:266, 1936.

A polysaccharide from Ascaris lumbricoides (of the hog) has been isolated and purified. Its general chemical characteristics and composition may be summarized as follows:

Before acid hydrolysis it is very soluble in hot or cold water and forms a neutral opalescent solution which gives a red-brown iodine reaction but no reaction to color tests for protein. It is precipitated by barium and calcium hydroxides but not by mineral acids, sodium hydroxide or basic lead acetate. It is highly dextrorotatory, does not reduce Fehling's solution, contains no chemically detectable nitrogen and only a trace of ash.

After acid hydrolysis the hydrolysate shows a maximal reducing power of 94 per cent, calculated as dextrose, and has a specific rotation of approximately +57 degrees. It gives no color reactions for hexuronic acids, pentoses or ketoses. The hydrolysate is tentatively considered to consist entirely of dextrose.

Precipitin, cutaneous and anaphylactic tests indicate that the polysaccharide is capable of inducing the formation of specific antibody as well as of reacting with it specifically. The reactions are immunologically specific with respect to a similar polysaccharide from the sheep tapeworm. The immunologic properties of the polysaccharide are not affected by boiling in neutral solutions or by proteolytic enzymes. The ability of the polysaccharide to incite formation of specific antibody, i. e., functional antigenicity, is more easily destroyed by dilute acids and alkali than is the capacity to react with such antibody, i. e., test antigenicity.

The possibility that the immunologic activity of the polysaccharide is due to minute traces of protein is considered. The immunologic relationship found between the polysaccharide and the closely associated water-soluble protein fraction is described and may be summarized as follows: In precipitin tests antiwhole-worm serum precipitates both the polysaccharide and the protein. Absorption of such antiserum with protein removes the precipitin for the protein but not that for the polysaccharide. Absorption of such antiserum with the polysaccharide removes the precipitin for the polysaccharide but not that for the protein. The addition of protein to antipolysaccharide serum produces no precipitate but decreases the activity of the latter toward the polysaccharide. Antipolysaccharide serum reacts with the polysaccharide but not with the protein, and antiprotein serum reacts

with the protein but not with the polysaccharide. In anaphylactic tests guinea-pigs sensitized with the polysaccharide are more sensitive to the polysaccharide than to the protein. The minimal sensitizing dose is 0.001 Gm. when tests for anaphylaxis are made with the protein, but only 0.00001 Gm. when tests are made with the polysaccharide. Guinea-pigs sensitized with the protein are more sensitive to the protein than to the polysaccharide. The minimal sensitizing dose is 0.001 Gm. when tests are made with the polysaccharide, but only 10^{-8} Gm. when tests are made with the protein. Cross-reactions between the two fractions can, for the most part, be accounted for by the presence of a detectable amount of the polysaccharide in the protein fraction.

The results obtained so far indicate not only the immunologic significance of polysaccharides from animal parasites but also a source from which large quantities of such a polysaccharide can be obtained for immuno-chemical study.

FROM THE AUTHOR'S SUMMARY.

LYSOZYME. M. PINNER and M. VOLDRICH, J. Infect. Dis. **60**:6, 1937.

A bacillus is described that is particularly susceptible to the action of lysozyme. Pleural effusions from tuberculous patients contain lysozyme in relatively high concentration. Under appropriate conditions secondary growth appears following lysis, but there is a definite interval between lysis and secondary growth, during which bacilli cannot be cultured on mediums suitable for their growth. During this "sterile" phase the bacilli exist apparently in a biologically altered state, probably in the form of large gram-positive cocci. Unpigmented rough dissociates were observed to arise from the original yellow smooth strain; the latter occurred more frequently in the secondary growth following lysis than in routine transplants; the latter were obtained exclusively following lysis.

FROM THE AUTHORS' SUMMARY.

LINKAGE RELATION OF ALLERGIC DISEASE, BLOOD GROUPS, M-N TYPES AND EYE COLOR IN MAN. I. ZIEVE, A. S. WIENER and J. H. FRIES, Ann. Eugenics **7**:163, 1936.

In fifty-five complete families each member was studied from the standpoint of allergic disease, blood groups, M-N types and color of the eyes. Statistical analysis failed to reveal any evidence of linkage among genes determining these various traits.

A. S. WIENER.

ANTIBACTERIAL IMMUNITY TO INFECTION WITH HEMOLYTIC STREPTOCOCCI IN RABBITS. T. C. STAMP, Brit. J. Exper. Path. **17**:391, 1936.

Immunity, believed to be mainly antibacterial to infection with hemolytic streptococci, may be developed in rabbits against intravenous and intradermal infection with the homologous strain. There is evidence that immunity to intravenous infection is developed before that to intradermal infection. Preliminary experiments indicate that this immunity may be passively transferred to normal rabbits and that it is not effective against infection with a heterologous strain.

FROM THE AUTHOR'S SUMMARY.

THE PATHOGENICITY AND IMMUNIZING POWER OF EGG VIRUS FOR FERRETS AND MICE. F. M. BURNET, Brit. J. Exper. Path. **18**:37, 1937.

Egg-passage influenza virus administered intranasally to mice produces, when it gives rise to any lesions at all, small areas of consolidation only, but it effectively immunizes the mice against large doses of highly active mouse-passage virus. Immunity can be produced by a very small dose of egg virus and appears between the seventh and tenth day after inoculation. The ferrets usually show no symptoms or a rise in temperature; occasionally an atypical "single spike" rise in

temperature occurs. Immunity of high grade, demonstrable either by direct inoculation or by titration of serum for specific antibody, regularly follows such inoculation. Unlike typical influenza of ferrets, the infection induced by egg virus is not infectious through contact with another ferret.

FROM THE AUTHOR'S SUMMARY.

THE LUNG IN SUBCUTANEOUS IMMUNIZATION. P. DE BOISSEZON, Ann. Inst. Pasteur **56**:597, 1936.

From histologic studies of the lung during artificial immunization the author concluded that the cells of the pulmonary histiocyte system were active in immunization, as are assumed to be the cells of the spleen and of the liver.

M. S. MARSHALL.

TUBERCULOUS ALLERGY AND ANAPHYLAXIS. E. CARLINFANTI, Ann. Inst. Pasteur **57**:134, 1936.

A study of antigens of tubercle bacilli did not give evidence sufficient to conclude that the mechanisms of the tuberculin reaction and anaphylaxis are similar. There existed an unstable stage in some tuberculous guinea-pigs sensitized to horse serum which simulated allergy to tuberculin. Local allergic reactions, like anaphylactic reactions, were not strictly specific, and a lasting state of densitization was not apparent in either case. But passive transfer of anaphylactic reactivity occurred regularly, whereas the allergic state was not transmitted. It is suggested that the rate of absorption of antigen may explain the differences apparent in the two types of phenomena.

M. S. MARSHALL.

MODIFICATION OF ANAPHYLACTIC SHOCK BY VITAMIN C. H. LEMKE, Monatschr. f. Kinderh. **67**:244, 1936.

Lemke observed that in children treated with vitamin C the incidence of serum disease was decreased. To clarify this action he made experiments on guinea-pigs and found that cevitamic acid inhibited sensitization as well as shock following reinfection of antigen into sensitized animals.

MENINGEAL REACTIONS IN ERYTHEMA NODOSUM. D. VON MORITZ, Monatschr. f. Kinderh. **67**:255, 1936.

Erythema nodosum is regarded as a general reaction which may be associated with meningeal symptoms in which increased pressure of the cerebrospinal fluid plays a part.

Tumors

THE CARCINOGENIC ACTION OF CERTAIN ESTROGENIC HORMONES. A. LACASSAGNE, Am. J. Cancer **28**:735, 1936.

The estrogenic substances theelin, equilin and equilenin caused characteristic changes in the mammary gland, uterus, prostate and hypophysis of the mouse. Theelin and equilin possessed equal carcinogenic powers, but the former produced marked proliferation in the mammary gland and hypophysis. Strains of mice which were little subject to, or refractory to, spontaneous mammary cancer showed delayed changes in the breast and hypophysis after treatment with the estrogenic hormones in comparison with strains highly susceptible to spontaneous mammary cancer. Combined injection of theelin and hypophysial extract produced in two strains of mice refractory to cancer epithelioma of the uterus, myosarcoma of the bladder and lymphosarcoma.

FREDERICK STENN.

BREAKING-DOWN OF THE RESISTANCE OF MICE OF ONE STRAIN TO THE TRANSPLANTATION OF TUMORS FROM MICE OF ANOTHER STRAIN. M. R. LEWIS and E. G. LICHTENSTEIN, Am. J. Cancer **28**:746, 1936.

The breaking-down of the resistance of mice of one strain to the transplantation of the 1, 2, 5, 6-dibenzanthracene tumors from mice of other strains by repeatedly inoculating the tumor tissue depended on the type of tumor used. Repeated inoculations of mice with tumors of an alien strain of mice resulted in five tumors: PHS 20 in BA mice, BA6 in C_3H mice, C_3H4 in BA mice, C_3H25 in BA mice and C_3H11 in BA mice. These were transplantable in more than one strain of mice. Those mice which remained refractory to the growth of tumors from the alien strain of mice and those in which the transplanted tumors grew and later regressed were not immune to the growth of tumors from their own strain of mice.

FROM THE AUTHORS' SUMMARY.

RÔLES OF HEREDITY AND SOMATIC MUTATION IN THE ORIGIN OF MALIGNANCY. W. F. DUNNING, M. R. CURTIS and F. D. BULLOCK, Am. J. Cancer **28**:681, 1936.

With a 1 per cent solution of dibenzanthracene and benzpyrene in warm paraffin malignant tumors were produced in rats and mice. The dose of the chemical determined the time of the malignant change. The change was not dependent on age, sex or genetic constitution of the host. Young hosts showed development of the tumors later than older ones. The histogenesis of the tumors seemed to be determined by the accidental exposure of the various types of cells to the irritant.

FREDERICK STENN.

THE IMPORTANCE OF STATISTICAL INVESTIGATIONS IN THE CAMPAIGN AGAINST CANCER. W. CRAMER, Am. J. Cancer **29**:1, 1937.

Experimental investigation of carcinogenesis has revealed two different and largely independent aspects of the etiology of cancer: the proximate cause of cancer, i. e., the intimate cellular changes which take place when a normal cell becomes malignant, and the remote causes of cancer, i. e., the various factors and conditions capable of bringing about this intimate cellular change. Cancer in man is a phenomenon of which the end-results are represented by the statistics on the mortality from cancer while the beginning of the phenomenon is unknown. The statistics are not likely to give any information on the proximate cause of cancer, but they are the most valuable and almost the only material available for the study of the remote causes. The statistics represent a material comprising at least 200,000 cases every year, if one restricts oneself to those countries from which reliable statistics are available, and this material presents data which cannot be obtained from observations on animals either in similar number or in regard to the special conditions of life peculiar to man.

Occupational cancer is an example of cancer the remote causes of which have been identified from an analysis of statistical data. This form of cancer has thus become preventable.

Statistical analysis of the mortality from cancer according to organs and age groups involved shows, first, that from the point of view of the remote causes cancer is not a disease all forms of which have common etiology, but that the etiologic factors vary with the organ involved. Second, the increase in the total mortality from cancer which remains after the necessary statistical corrections have been made on account of the greater longevity of the populations in civilized countries is not distributed equally over the different involved organs and age groups. In some organs the frequency of cancer has diminished; in some it has remained stationary; in a third group it has increased. The increase is found in the older age groups, while in the younger age groups the incidence has either remained stationary or has diminished.

Further analysis of the mortality from cancer according to exposed sites and nonexposed sites has shown that in the exposed sites the incidence rapidly increases as one descends in the social scale. This proves that for the exposed sites, which are responsible for the bulk of the total mortality from cancer, some of the remote causes are to be found among the habits and conditions of life of the lower social classes, that such factors can be avoided and are being avoided by the upper social classes and that therefore a large fraction of the total incidence of cancer is preventable. There is, in fact, "social cancer" as there is "occupational cancer." If occupational cancer is preventable, social cancer, to which a large share of the total mortality from cancer may be ascribed, should also be preventable.

So far the existence of social cancer has been demonstrated for only two countries, England and Bavaria. It will be necessary to extend this analysis to other countries. By restricting the search for the remote causes of cancer in the exposed sites to differences in the habits and conditions of life in the social classes of these two countries, it will become possible to identify some of the causes by further statistical analysis and detailed investigations into the previous history of patients who have cancer.

Another method of obtaining from statistical data information concerning the remote causes of cancer is by a comparison of the statistics on cancer mortality as reported from different countries provided that they are comparable. The following examples are referred to: the exceptional frequency among natives in the Far East of primary cancer of the liver cells, which is always associated with cirrhosis of the liver; the exceptional frequency in Japanese women of uterine cancer in contrast with an exceptional rarity of breast cancer; the exceptional frequency in Switzerland of cancer of the esophagus in men.

The present knowledge of the importance of hereditary factors in the etiology of cancer can perhaps be summarized best as follows: Cancer as a disease is not inherited; only susceptibility to development of cancer in response to persistent carcinogenic stimuli can be inherited. In man the etiologic significance of this factor is, apart from certain rare conditions, not sufficiently important to condemn the offspring of a cancerous ancestry to the probability that cancer will develop. But from the point of view of the diagnostician a history of cancer in the family of a patient when there is a possibility of malignant disease and the diagnosis is doubtful should be considered as a factor weighing in favor of the diagnosis of cancer.

Statistics on mortality from cancer if reliably collected and suitably analyzed with the necessary statistical corrections present a method of identifying some of the remote causes of cancer in man for some of those organs cancer of which takes the heaviest share in the total mortality from this disease—a method, in other words, to make a considerable part of the incidence of cancer preventable. Such an objective, so clearly outlined, is well worth striving for. It is difficult, in face of the evidence, to understand and be patient with the paralyzing pessimism which still prevails concerning the possibility of applying the advance in knowledge of the etiology of cancer to the solution of the fundamental problem—the prevention of cancer in man.

FROM THE AUTHOR'S SUMMARY.

RECKLINGHAUSEN'S NEUROFIBROMATOSIS. J. C. SHARPE and R. H. YOUNG, Arch. Int. Med. **59**:299, 1937.

The clinical features that any particular patient may present will be dependent on his age, the congenital factors and his individual sensitivity to stimulating influences. Of all the influences studied in the thirty-one cases, pregnancy was the most stimulative to progression of the disease. This effect has been mentioned in the past, but its dramatic nature has not been fully appreciated. In the management of this disease, which is hereditary in a large percentage of cases and which is without a beneficial form of treatment, it seems that avoidance of pregnancy

affords the chief opportunity for control and arrest. It is hoped that further attention to the history of the disease during the life of the affected subject rather than a consideration of the more classic static nosologic cross-section of the disease which the patient presents at any one period of life will be productive of a more helpful management.

FROM THE AUTHORS' SUMMARY.

Medicolegal Pathology

GROUP-SPECIFIC PROPERTIES OF VERNIX CASEOSA. F. TARSITANO, Folia med. **22**:642, 1936.

Tarsitano concludes that vernix caseosa has group-specific properties as shown by the absorption of specific iso-agglutinins from blood serum. There is perfect correspondence between the blood group to which the infant belongs and the group of the vernix. The quantitative value of absorption by vernix caseosa is low compared with that of the blood erythrocytes of the infant. The specific absorption properties can be used in medicolegal procedures for identification and other aims.

THE DIAGNOSIS OF DEATH BY DROWNING THROUGH THE DEMONSTRATION OF PLANKTON ORGANISMS IN THE LUNGS AND DUODENUM. B. KASPAREK, Deutsche Ztschr. f. d. ges. gerichtl. Med. **27**:132, 1936.

The question frequently arises as to whether water in the lungs was aspirated in drowning or entered the air passages of the corpse. The oft-cited contention that water inhaled by a drowning person penetrates to the alveoli generally, while water entering the body after death flows by gravity to the larger bronchi and the dependent lobes has been corroborated. The distribution of barium or bismuth preparations added to water can be demonstrated roentgenologically to prove these points. Starch, coal dust, milk and algae have been recovered from the alveoli of animals drowned in water containing such indicators. The demonstration of algae in human beings has been more difficult, however, because cold weather reduces the number of such organisms in streams and lakes and decomposition reduces their chlorophyll content. By expressing the fluid found in the peripheral alveoli of the lung, algae and diatoms may be found in small numbers. Digestion by acid or ashing of the lung may yield more consistent results. In this manner algae were demonstrated in the lungs of eleven of twelve bodies recovered from water. The one body in which the results were negative had been drowned in winter, lay in water six months and was reduced to adipocere.

The investigations on water found in the duodenum were less conclusive. It is assumed that an intact pyloric ring retains water swallowed by the drowning, in the stomach. Only after decomposition has set in does the pylorus relax and permit the water to flow into the duodenum. The examination of duodenal contents for algae is rendered difficult because chlorophyll containing food may be present. The acid digestion and ashing processes may aid in the discovery of algae and diatoms in such content.

GEORGE RUKSTINAT.

A CLINICO-ANATOMIC AND SPECTROGRAPHIC INVESTIGATION OF THE CENTRAL NERVOUS SYSTEM IN ACUTE METAL POISONING. A. ESSER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **27**:253, 1937.

The initial section of this report deals with the significance of the metals in toxicology. At present, strontium, uranium and osmium play practically no rôles as poisonous agents, and nickel, cobalt and platinum, only minor ones. Murder is most often committed by the administration of substances containing barium, aluminum, thallium, copper, chromium, lead, iron, or, most frequently, mercury. Suicides are often committed with compounds of barium, thallium, copper or manganese, but chromium, lead and especially zinc and mercury are most frequently chosen for this purpose. Among laymen mercury assumes primary importance

as a poison; zinc and lead follow in close order. Manganese has become increasingly popular as an aid to suicide with Hungarian women in the last ten years. The most popular abortifacients are lead salts, but many other metallic salts have been used for this purpose. The widespread use of thallium and barium in rat poison has led to their use as a lethal foodstuff, also to death through inadvertent ingestion.

Clinical observations of men and animals suffering from acute metal poisoning have been in agreement as concerns the symptomatology. The common symptoms are convulsions, mostly of the tonic-clonic variety. These are followed by flaccid paralysis, which starts in the legs and progresses upward until respiratory failure causes death.

The cells in the anterior horns of the spinal cord and the cells of the medulla are most often damaged by metals. The brain is less affected by pure degeneration in Nissl's sense. In the vascular apparatus there is severe change in hyperemia, stasis, hemorrhage and endothelial swelling. Resorptive processes can always be demonstrated in the glia after twelve hours. The degree and extent of the paralysis parallel the degree of damage of the ganglion cells. The anatomic alterations are not dependent on the circulatory disturbances but are the direct effect of the poison on the central nervous system. Since the clinico-anatomic changes are the same for a variety of metals, it is impossible to correlate symptoms and bodily content of poison for any one metal. In thallium poisoning, there are sensory and psychotic disturbances which are lacking with other metals.

Spectrographic examinations disclosed only traces of poison in the central nervous system, and therefore the damage of the ganglion cells is probably the result of the metal coursing in the blood stream. Examination of the subcutaneous tissues of guinea-pigs with condenser and high frequency spectrographs demonstrated barium, copper, silver, gold, chromium, cobalt and nickel easily after poisoning with their salts. Zinc, strontium and aluminum could be detected to some extent; detection of cadmium and thallium was unsatisfactory; mercury gave questionable results; and tin, lead, uranium and manganese were not demonstrable.

GEORGE J. RUKSTINAT.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

FRANCIS D. GUNN, *President*

Regular Monthly Meeting, Oct. 11, 1937

EDWIN F. HIRSCH, *Secretary*

PRESIDENTIAL ADDRESS: CHANGING CONCEPTS IN LOBAR PNEUMONIA. FRANCIS D. GUNN.

Among the more recent contributions to knowledge of the inciting agents, pathogenesis, immune reactions and mechanism of recovery in pneumonia, no small part has come from the field of bacteriology, where greater emphasis on the biologic characteristics of bacteria, rather than on the morphology and the ordinary cultural features, has contributed greatly to the better understanding of pneumococcic infections and of immunity, with the emphasis shifted largely to cellular immunity.

The time-honored concept of the production of pneumonia by the ordinary bacterial flora of the upper respiratory tract has given way to the all but finally proved fact that disease-producing power is a property exclusively of specific virulent types of pneumococci. This phase of the problem has been clarified by the use of more accurate methods in determining the types of pneumococci responsible for disease and by the recognition of many specific pathogenic types in group IV (Avery), for which a large part of the credit is due Cooper and her associates. A reappraisal of older data and an accumulation of new facts concerning the relative frequency of the various types of pneumococci in pneumonia are already well under way, and in 1937 Finland and his associates reported on anatomic and bacteriologic findings in 3,682 cases of pneumococci infections with 764 necropsies. In their cases of lobar pneumonia with necropsy, 90 per cent were due to seven more common types, I, III, II, V, VII, VIII and IV, in the order of frequency, of which the first three occurred 67 per cent. A certain general relationship between the type of pneumococci and the anatomic form of the lesions is indicated in human cases, infections with types I and II resulting in lobar pneumonia in over 80 per cent of cases and type III accounting for by far the greatest number (47 per cent) of cases classified as atypical in Finland's series. In experimental animals this relationship is not so clear. Certain host factors and the initial distribution of the infecting bacteria in the lung appear to be of equal or even greater importance in the determination of the form of the lesion.

With recognition of the disease as an infection of the lung by one or the other of several specific types of pneumococci, the problem of carriers of virulent types has assumed more importance. It is unusual to find one or more of the virulent types of pneumococci in the nose or pharynx of a normal healthy person unless he has been in contact with patients who had pneumonia, but in the presence of an epidermic, especially under the crowded conditions of the cities or in crowded army barracks, prisons and asylums for the insane, many apparently well persons may harbor virulent pneumococci. Why is it that such persons do not more frequently succumb to pulmonary infection? In other words, what are the conditions in the host under which pneumonia may be expected to arise? It has been shown experimentally that inoculation of the nose or nasopharynx of a susceptible animal is not sufficient to produce the disease with regularity, but if virulent pneumococci, even in minute doses, are introduced into the respiratory

bronchioles and alveoli, an exudative response such as that seen in human croupous pneumonia regularly ensues. It is now generally conceded on the basis of preponderant clinical and experimental evidence that lobar pneumonia is always the result of infection by the intrabronchial route.

The question which appears to be critical for the complete understanding of the pathogenesis is concerned with the mode of conveyance of pneumococci from the upper respiratory tract to the alveolar ductules and alveoli. The solution is suggested in part by the analysis of factors in various predisposing conditions, such as chilling of the body by unaccustomed exposure to cold, inspiration of dust or irritating gases, preceding infections of the upper respiratory tract, especially coryza, which Cole, Hall and others have observed to precede the onset of pneumonia in at least 50 per cent of cases. The two common factors which have been recognized are, first, the presence of greatly increased secretions owing to direct irritation of the mucous membranes or to nervous stimulation and, second, the production of hyperemia and edema in the parenchyma of the lung. The first factor has been stressed by Nungester and Jourdonais, who have supported with experimental evidence their contention that the presence of excessive quantities of mucinous secretions is conducive to aspiration of bacteria from the upper part of the respiratory tract into the parenchyma of the lung, where they give rise to pneumonia. A further effect of mucinous secretions is through their protective action on the pneumococci against immediate destruction by alveolar macrophages. There can be little doubt that viscid substances such as starch paste, sterilized gastric mucin and blood serum can enhance the effective pathogenicity of bacteria, especially in the lung, yet such substances are not absolutely essential in pneumonia for, with adequate doses of virulent pneumococci, the same results can be obtained experimentally without them. It seems reasonable to assume that extremely minute doses of bacteria, which without a protective menstruum would be insufficient to induce a progressive lesion, are protected from phagocytosis and destruction for a few hours, during which time they proliferate actively until they reach a sufficient number and concentration. Thus the action of viscous fluid on subminimal doses would have the same results as an initial aspiration of much larger doses.

The second factor, that of edema, is concerned both with the mechanism of initiation of the primary lesion and with the mechanism of spread, once the process has begun. However, primary local edema, while assisting in the establishment of the initial lesion in cases in which the dosage of pneumococci is small, thus accounting for the mechanism of certain predisposing factors, is not essential for the initiation of the disease, since virulent pneumococci in sufficient dosage are capable of bringing about a local irritation of the parenchyma which results quickly in inflammatory edema.

Since the morphologic studies of Loeschcke on lungs from cases of pneumonia in an early stage it seems probable that in the majority of cases of lobar pneumonia the initial lesion arises in the peripheral portion of the lung, most frequently near the dorsolateral border of a lower lobe, and spreads in a wavelike manner by the outpouring of inflammatory edema fluid and not, as maintained by Blake and Cecil, as a cellulitis of the peribronchial connective tissue and alveolar septums, beginning in the region of the hilus. The importance of collateral edema in the spread of pneumococcic infection has been demonstrated by the experiments of Rhoads and Goodner on so-called "dermal pneumonia" and is supported by the observations on the pathogenesis of experimental pneumonia in dogs by Robertson, Coggeshall and Terrell and in rats by Gunn and Nungester.

A description of the sequence of events in the development of the pneumonic lesion and the present concept of its mechanism will be omitted, as this phase has been previously published in the ARCHIVES OF PATHOLOGY (**21**:813, 1936).

A consideration of the manner of resolution of the exudate brings one to another phase in which the emphasis is shifting. Specifically, more importance is now being attributed to the part played by macrophages in the removal of the exudate whereas in the past resolution was considered to be exclusively a function of

leukocytic ferments. After the full development of the lesion, with maximal precipitation of fibrin in the alveoli, gradual disappearance of the leukocytic component of the exudate has been observed to take place. Some of the loss of leukocytes is undoubtedly through disintegration but, in the opinion of Loeschcke, the loss is due largely to emigration of surviving leukocytes from areas in which pneumococci have been destroyed into zones of more recently formed exudate in which pneumococci or their products still persist. This opinion is supported by observations on experimental pneumonia. Fibrin-rich and cell-poor areas appear even before the stage of shrinkage of fibrin, which in experimental pneumonia is seen first about the fifth day of the disease. It is out of the question that ferments from disintegrating leukocytes could be responsible for the solution of fibrin in these areas, since leukocytes have all but disappeared long before the fibrin begins to diminish. What appears actually to take place after the stage of shrinkage of fibrin is, first, a second stage of engorgement of alveolar capillaries as the intra-alveolar pressure is relaxed, a more or less prominent extravasation of blood accompanying the relaxation of the capillary walls, and a marked proliferation of mononuclear phagocytes. It is the striking increment of these alveolar phagocytes that is constantly accompanied by diminution in size of the fibrin masses in the alveoli.

Just as the mobilization of histiocytes is necessary for the complete sterilization of the lesion and for the solution of the fibrin clots, it appears increasingly probable that the histiocytes are indispensable for the development of immunity. It has been demonstrated experimentally by Stuppy, Cannon and Falk, by Coggeshall and Robertson and by others that the mechanism of pulmonary immunity to the pneumococcus is through an actual numerical increase of functionally active histiocytes and through a specifically increased reactivity of these cells. Evidence of specific immunity appears in the lung long before immune bodies are demonstrable in the serum of previously nonimmune animals. The conclusion is almost inescapable that immune bodies are produced locally in the infected tissue, probably by the histiocytes themselves, and are present in quantities which are adequate for the sterilization of the lesion through the agency of the phagocytes much earlier than the time of appearance of specific antibodies in the circulating blood.

Aortic Stenosis, Atresia and Adult Coarctation in a Triloculate Heart. George J. Rukstinat.

The heart was obtained from the body of a girl who was cyanotic and dyspneic at birth and lived three days. The main observations at necropsy were: marked venous engorgement, fetal atelectasis involving both lungs and anomalies of the heart and aorta. The heart was 4.5 cm. from apex to base and 3.6 cm. broad. The pulmonary artery was dilated up to 21 mm. in circumference in its proximal 14 mm., gave off the right pulmonary branch 8 mm. from its origin and the left at 9 mm., and then narrowed gradually until it was only 10 mm. in circumference. The pulmonary leaflets were normal, and 15 mm. distal to them the artery was partially closed by a diaphragm with a central oval opening 1 mm. wide and 2.5 mm. high. The partition had a slope of 45 degrees toward its anterior distal edge. Promixal to it the superior edge of the vessel formed a trilocular bulge, from which started the large vessels of the aortic arch. Posteriorly and at the proximal edge of the perforated diaphragm was an opening 0.5 mm. in diameter, which led into an aorta with a lumen 0.5 mm. in diameter. This pursued a normal course and had three semilunar cusps, each 0.7 mm. in width, but had no opening into the single ventricle. There were openings for the coronary arteries from the anterior and posterior sinuses of Valsalva. Distal to the diaphragm of its lumen, the aorta continued, giving off the intercostal arteries and other branches in normal fashion.

The heart possessed two auricles. The venae cavae entered the large right chamber, and two groups of pulmonary veins entered the left. An opening between the auricles was 1 cm. in diameter. Heavy muscular ridges 5 mm. broad and 2 mm. high formed the edge of this foramen ovale in the basal and contiguous

halves of the anterior and posterior quadrants. From them, thin endocardial filaments extended to the opposite periphery and formed a wide-meshed net. The single ventricle had no remnant of a septum and contained a three-segment auriculoventricular valve with one orifice, 2.7 cm. in diameter. Nine papillary projections gave rise to chordae tendineae. Five muscles supplied only one chorda, while the others had from four to seven inserting into the leaflets.

Histologically, there was no inflammation of the aorta, pulmonary artery, myocardium or valve leaflets. The condition was regarded, therefore, as developmental in origin and of an unusual nature. The occurrence of this anomaly in a child of 3 days is one of the earliest on record.

TITERS OF ISO-AGGLUTININS IN SERUM DISEASE, IN LEUKEMIA AND AFTER BLOOD TRANSFUSION. I. DAVIDSOHN.

A study of the distribution of titers among 517 normal persons and ambulatory patients with chronic disease confirmed the previously reported greater frequency of higher titers for the anti-A iso-agglutinins in blood groups B and O as compared with the anti-B iso-agglutinins in blood groups A and O. This indicates that there is a relatively greater danger when blood from the so-called universal donors with high titers of iso-agglutinins is used for type A patients than when it is used for type B patients. High iso-agglutinin titers are most common among young persons and become less frequent with advancing age. The distribution of the titers is similar in both sexes. The prevalence of low titers of iso-agglutinins in leukemia was confirmed, but only in the chronic form of the disease, particularly in patients who did not receive roentgen therapy. Most patients with acute leukemia and patients with chronic leukemia who received intensive roentgen therapy had normal or even slightly elevated titers. Very high titers were observed in many cases of serum disease. Patients with serum disease may be used to supply serums with high titers for blood grouping tests. In infectious mononucleosis the titers of iso-agglutinins are within the range of normal variations.

DISCUSSION

VICTOR LEVINE: I have encountered some difficulty in obtaining suitable donors for patients with a low erythrocyte content when cross-matching was done. Is there a reason for this?

I. DAVIDSOHN: I have had the same experience, but the clumping is mainly marked rouleaux formation. Dilution of the recipient's serum with an equal volume of solution of sodium chloride corrects the difficulty. There is danger in chronic leukemia that the anti-B agglutinins in an O serum are too weak to agglutinate the cells in the usual tests.

HISTOLOGY OF THE BRAIN IN EXPERIMENTAL HYPERINSULINISM. ARTHUR WEIL, ERICH LIEBERT and GERT HEILBRUNN.

The procedures of the insulin shock therapy for dementia praecox were closely imitated in rabbits. Gradually increased amounts of insulin were injected intramuscularly every week day until the dose was found which would produce a convulsive seizure. The seizure was immediately interrupted by giving dextrose intravenously or by stomach tube. The rabbits were allowed to die during a seizure, or they were killed after different periods of survival. The average dose for the production of convulsive seizures was about 2.5 units per kilogram of weight. Sensitization to the effect of insulin occurred but disappeared again after about two weeks.

Up to 70 units of insulin injected over different periods did not produce microscopically demonstrable damage to the brain. From 70 to 150 doses injected caused minor histologic changes, while doses of from 200 to 400 units injected over a period of two months severely damaged the cerebral neurons. There was a difference in the histologic changes of brains from rabbits which had died during a convulsive seizure as compared with the brains of those which were allowed to

survive for weeks or months. In the first group severe ganglion cell disease in the form of liquefaction, vacuolization and homogenization was predominant. The second group was characterized by marked shrinkage of cytoplasm and nuclei. Diminution in the number of neurons in different cortical areas was found in both groups to a more or less marked degree.

The pathologic changes seem to be the result of anoxemia, not anoxemia from lack of oxygen following vascular lesions, but "intracellular anoxemia," that is, the inability to utilize oxygen in the presence of large doses of insulin.

This article will appear in full in a later issue of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY.

DISCUSSION

F. D. GUNN: Since insulin in high doses is toxic for nerve cells, one may wonder in what dosage it is not toxic.

S. ROSENTHAL: How do you explain the benefit observed in patients with mental diseases after the insulin shock therapy?

A. WEIL: The doses of insulin used in these experiments were far beyond the physiologic range. There is no satisfactory explanation as yet for the clinical effects noted.

Book Reviews

The Patient and the Weather. By William F. Petersen, M.D., with the assistance of Margaret E. Milliken, S.M. Volume 4, Part 1: Organic Disease: Cardio-Vascular-Renal Disease, Including a Chapter on Experimental Endocarditis by Alexander J. Nedzel. Cloth. Price, $10. Pp. 663, with 443 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1937.

Petersen introduces this formidable part 1 of volume 4 of his series of monographs with an "Asclepian ramble" through the fields of clinical medicine as presented in newspapers and journals. When clinical reports are accurately enough dated he has found that clinical episodes are correlated with the meteorological conditions of the locality at the time. In this opening chapter he lays aside the somber Prince Albert coat of professional and professorial seriousness and, tongue in cheek, does a bit of fun-poking and nose-thumbing at the clinicians. It was evidently the perversion of atmospheric flow connoted by what he terms the "laryngeal constipation" of the psychoanalysts that drove old Asclepias from beneath the author's hospitable rooftree back to the sweeter winds of his native Olympus. Such section headings in the first chapter as "The Death of Mr. Traylor," "The Case of Patricia Maguire" and "A Celebrated Case . . ." in chapter 7 must not lead the unwary reader to believe that he is going to read a collection of mystery stories which he will not be able to put aside until he has completed the volume.

In chapter 2 Petersen correlates the meteorological state with functional reactions, in a wide number and variety of personal observations. Then follow four chapters on cardiovascular-renal disease, in which he discusses the various aspects of this complicated pathologic state. Detailed reports of cases illustrate the precipitation of major clinical episodes by polar infalls and other meteorological changes.

The thesis elucidated in the discussion is that the individual reacts, in many ways rhythmically, to his meteorological environment, the reactions varying within normal physiologic limits according to the constitutional makeup of the individual, that disintegration of reactions and maladjustment to environment lead to functional abnormality and that continuation of the process leads to the anatomic abnormalities so frequently observed in the cardiovascular-renal system. Or as Petersen put it: "I am primarily interested in the demonstration of one fact—that organic disease may take its origin from subminimal environmental stimuli—interested in the very beginning of the diseases of the major organs" (p. ix). He says further: "I shall present the evidence that the self-same mechanism that precipitates the final clinical symptomatology is of significance in initiating the earlier disturbances of integration that ultimately cause the clinical entities that we recognize as disease" (p. xviii).

The evidence is presented in the form of many clinical reports, recorded with meticulous detail, of clinical episodes and laboratory findings. In an early page he warns that "we shall have to wade through many pages to demonstrate the very simple fact that our old Asclepias is still a very potent God" (p. 105). It must be admitted that the wading is a rather wearisome excursion. But wading through printed clinical records never is as much fun as wading a trout-stream with rod and reel and creel—when the weather is propitious.

The final chapter, a brief one by A. J. Nedzel, describes experimental production of bacterial endocarditis in dogs. Essential for localization of bacteria, in this process, is increased adhesiveness of the valvular endocardium, which is brought about by pressor episodes such as are mediated in man by the weather. The chapter is illustrated by thirty-eight excellent half-tones.

"It would be quite out of the range of these monographs to enter into a philosophical discussion of the medicine of today," writes Petersen (p. ix). Although

he mainly presents data and their interpretation, he does, in the preface of each volume, philosophize about the medicine of today as it is and as he thinks it ought to be.

Clinical Parasitology. By Charles Franklin Craig, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Colonel, U. S. Army (Retired), D.S.M., professor of tropical medicine, Tulane University of Louisiana, New Orleans, and Ernest Carroll Faust, M.A., Ph.D., professor of parasitology in the department of tropical medicine, Tulane University of Lousiana, New Orleans. Cloth. Price, $8.50. Pp. 733, with 243 illustrations. Philadelphia: Lea & Febiger, 1937.

The present volume is designed not only for the use of practicing physicians, but for use in courses in parasitology whether these are in the medical or in the academic curriculum. Its subject matter is limited to the animal parasites and is divided into three sections covering the protozoa, the helminths and the arthropods, with a technical appendix and a short selected list of references to the literature. Under the heading of each parasite the authors have given accounts of the nomenclature, history, geographic distribution, morphology, life-history, epidemiology, methods of transmission, pathology, symptomatology, diagnosis, treatment and pretention. The arthropods are treated very fully not only as parasites but as venomous animals and carriers of disease. The various accounts are concise and accurate and are supplemented by excellent illustrations throughout the text. The chief criticism that can be brought against this book is that it may be designed for too large a public. Thus, the practicing physician might desire a more detailed description of certain therapeutic measures and other clinical aspects, and the academic parasitologist, a somewhat greater emphasis on various zoologic aspects of parasitism. Such criticisms are, however, matters of opinion. The authors have written an excellent book which contains much more parasitologic material than the usual treatise on tropical medicine and considerably more clinical details than the usual zoologic texbook.

The Therapeutic Problem in Bowel Obstructions. By Owen H. Wangensteen, M.D., Ph.D. Price, $6. Pp. 360, with 90 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

Section one of this book is a reprint of the essay that won the quinquennial Samuel D. Gross Prize for 1935, awarded by the Philadelphia Academy of Surgery. This is a thorough and interesting analysis of the pathologic physiology accompanying obstructions. The chapters in this section deal with the following topics: the character and source of the distention; the manifestations of distention on the bowel wall; absorption in obstruction; the significance of the loss of blood in strangulating obstructions; recognition of obstruction of the bowel; treatment of obstruction. Each of these subjects is illustrated by case histories or examples of experimental work on animals and patients. Section one is thorough but not tiring. It will be read with real interest by general practitioners and surgeons of long experience.

Sections two and three are entitled, "General Considerations of Diagnosis and Treatment in Bowel Obstruction" and "The Special Obstructions." These give a detailed description in the usual textbook style. There is a wealth of material here, most of which is of interest to physicians in general. The continuous suction treatment and its use in obstructions are covered thoroughly. The limitations of suction treatment are sharply drawn.

Books Received

SOME FUNDAMENTAL ASPECTS OF THE CANCER PROBLEM. SYMPOSIUM SPONSORED BY THE SECTION ON MEDICAL SCIENCES OF THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, ATLANTIC CITY, NEW JERSEY, DECEMBER 29, 1936-JANUARY 1, 1937. Edited by Henry Baldwin Ward. Publication Committee: William Charles White, Chairman; Clarence Cook Little, Esmond R. Long, Vincent du Vigneaud, Carl Voegtlin. Cloth. Price, $2.50. Pp. 248, with illustrations. New York: The Science Press, 1937.

THE THERAPEUTIC PROBLEM IN BOWEL OBSTRUCTIONS. Owen H. Wangensteen, M.D., Ph.D., Professor of Surgery, University of Minnesota, and Surgeon-in-Chief, University of Minnesota Hospital. Cloth. Price, $6. Pp. 360, with 90 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

ANNUAL REPORT OF THE INSTITUTE FOR MEDICAL RESEARCH FOR THE YEAR 1936. Lewthwaite, Acting Director, Institute for Medical Research, Federated Malay States, Kuala Lumpur. Paper. Price, $1. Kuala Lumpur: Federated Malay States Government Press, 1937.

ESPERIMENTI DI VACCINAZIONE ANTITUBERCOLARE. ESEGUITI SOTTO IL CONTROLLO DEL COMITADO TECNICO-SCIENTIFICO DELL'ISTITUTO VACCINOGENO ANTITUBERCOLARE. Relazione Stesa dal Prof. Alberto Ascoli. Presentazione di S. E. Sante De-Blasi, Presidente del Comitato per la Medicina del Consiglio Nazionale delle Ricerche. Paper. Milan: Laboratori di Patologia Comparata della Regia Universita e Istituto Vaccinogeno Antitubercolare di Milano, 1936.

THE POSTMORTEM EXAMINATION. Sidney Farber, M.D., Associate in Pathology, Harvard University Medical School, and Pathologist to the Infant's Hospital and the Children's Hospital, Boston. Cloth. Price, $3.50. Pp. 201, with 33 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

AN ANALYSIS OF THE RESULTS OF TREATMENT OF EARLY, LATENT, AND MUCO-CUTANEOUS TERTIARY SYPHILIS. W. R. Snodgrass and R. J. Peters. Medical Research Council, Special Report Series, no. 224. Paper. Price, 2 shillings. Pp. 126. London: His Majesty's Stationery Office, 1937.

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DECEMBER 1937

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 20, 1926, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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